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QUANTITATIVE PLUTONIUM MICRODISTRIBUTION IN BONE TISSUE OF VERTEBRA FROM A MAYAK WORKER

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Abstract

The purpose was to obtain quantitative data on plutonium microdistribution in different structural elements of human bone tissue for local dose assessment and dosimetric models validation. A sample of the thoracic vertebra was obtained from a former Mayak worker with a rather high plutonium burden. Additional information was obtained on occupational and exposure history, medical history, and measured plutonium content in organs. Plutonium was detected in bone sections from its fission tracks in polycarbonate film using neutron-induced autoradiography. Quantitative analysis of randomly selected microscopic fields on one of the autoradiographs was performed. Data included fission fragment tracks in different bone tissue and surface areas. Quantitative information on plutonium microdistribution in human bone tissue was obtained for the first time. From these data, quantitative relationship of plutonium decays in bone volume to decays on bone surface in cortical and trabecular fractions were defined as 2.0 and 0.4, correspondingly. The measured quantitative relationship of decays in bone volume to decays on bone surface does not coincide with recommended models for the cortical bone fraction by the International Commission on Radiological Protection. Biokinetic model parameters of extrapulmonary compartments might need to be adjusted after expansion of the data set on quantitative plutonium microdistribution in other bone types in human as well as other cases with different exposure patterns and types of plutonium.

Keywords

plutonium; skeleton; neutron-induced autoradiography

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INTRODUCTION

The skeleton is a repository for many metals and radionuclides (Priest and Van De Vyver, 1990) and thus is at risk for radiation effects. Plutonium is of particular importance because it is a potent carcinogen and is used in nuclear weapons and nuclear power engineering, as well as other applications. Once plutonium is in the systemic circulation, for example, it is primarily concentrated in the liver and the skeleton in humans (Suslova et al. 2002). Epidemiological studies of plutonium personnel cohort show the presence of a reliable correlation between radiation levels from incorporated plutonium and the risk of skeletal malignant tumors (Koshurnikova et al. 2000). Furthermore, these plutonium-induced skeletal tumors tend to appear at skeletal sites that differ from naturally occurring tumors (Miller et al. 2003). Other radionuclides that deposit in bone are also associated with skeletal cancers and include ^{224}Ra , ^{226}Ra , ^{228}Ra , ^{228}Th , ^{249}Cf , and ^{252}Cf (Lloyd et al. 1994).

Neutron-induced autoradiography (NIAR), also called “fission track autoradiography” (FTA), permits the identification and localization of very small amounts of plutonium in biological tissues (Becker and Johnson, 1970). In animal studies, the fission tracks present in the NIARs and the underlying tissue structures can be quantified resulting in estimates of plutonium concentrations and radiation doses to specific anatomical locations. These include structural bone elements and tissue compartments, (i.e. endosteal surfaces, bone tissue, bone marrow) (Wronski et al. 1980; Jee et al. 1972).

The purpose of this report was to present quantitative data on plutonium microdistribution in different areas of human bone tissue. These tissues were obtained from former workers at the Mayak Production Association, Ozyorsk, Russia. This approach should permit investigators to obtain detailed localization and distribution data for plutonium in the human. These data will allow researchers to make skeletal radiation dose assessment more precise, lead to improved radiation safety standards, and further our understanding of radiation-induced human cancers.

MATERIALS AND METHODS

The Southern Ural Biophysics Institute (SUBI) Russian Human Radiobiological Tissue Repository (RHRTR) (Muksinova et al. 2006) was the source of biological material for studying plutonium microdistribution in bone tissue. Bone tissue samples were obtained during the autopsy of former workers from the nuclear fuel cycle plant (Mayak) and are stored in separate storage containers in neutral formalin.

For the present study, the biological material of the case (identification number in the repository is 440) with high plutonium body burden (44 kBq) was selected. Personal medical and dosimetric information including radiation history, medical data, autopsy records as well as postmortem radiometry data of organs and tissues is shown in Table 1. The employee worked at the plutonium plant for 7 years as a chemist-technologist and generally had daily contact with relatively soluble plutonium-nitrate compounds. After being diagnosed with chronic radiation sickness, the individual was transferred to another work location for 6.5 years, but had the potential for contact with insoluble plutonium dioxide aerosols. The records indicated exposures to uranium compounds were not likely. The exposures to plutonium-nitrate compounds helps explain the relatively small fraction of plutonium retained in the lungs relative to other organs of this worker (Table 1).

Preparation of samples

A well-preserved sample of thoracic vertebra was obtained for the study. The sample had been stored in neutral formalin for 12 years. The vertebra was selected because the vertebral column

is a site with a higher propensity for plutonium-induced sarcomas in experimental animals (Miller et al. 1986; Lloyd et al. 1994) and humans (Miller 2002; Miller et al. 2003). Additionally, the vertebral bodies have a greater content of plutonium per unit bone mass than most other bones (Kathren et al. 1987). The tissue samples were dehydrated in ethyl alcohol at a concentration increasing sequentially from 40 to 100%. The dry bones were infiltrated with methyl methacrylate containing benzoyl peroxide as an activator. Infiltration was enhanced by several applications of vacuum to expel the air from the bone. Specimens were placed in a water bath at 37°C, and the temperature held constant until complete polymerization. Sections through the middle of the vertebral bodies were cut using a low-speed bone saw (Isomet, Buehler), polished with aluminum oxide to about 100 µm in thickness and cleaned in ultrapure water. The sections were soaked for 15 min in a 15% sodium borate solution, again rinsed in ultrapure water and allowed to dry in a dust-free environment.

Neutron-induced autoradiography

Neutron-induced autoradiography has an advantage over conventional autoradiography by decreasing the time necessary to attain a sufficient track density. Rather than waiting for a natural decay of the isotope with the registration of the alpha emission on a photographic film or emulsion, NIAR accelerates this by exposing the sections to thermal neutrons that will cause the ^{239}Pu to fission. The fission fragments are registered on plastic detectors, rather than a photographic film or emulsion, as previously described in greater detail (Jee et al. 1972; Bruenger et al. 1991). In addition, use of the NIAR is very practical to study plutonium distribution in bone tissue inasmuch as decalcification is not necessary. Decalcification results in plutonium “wash-out” from bone surfaces.

The bone sections were sandwiched between two Lexan polycarbonate detectors (International Plastics, Poughkeepsie, NY). The sections with their Lexan detectors were placed in a single container fabricated to fit in the port of the nuclear reactor. The container was then irradiated with thermal neutrons at a flux of 8×10^{12} neutron $\text{cm}^{-2} \text{s}^{-1}$ with a total neutron fluence of 9.6×10^{16} neutron cm^{-2} . This was done at the Massachusetts Institute of Technology Nuclear Reactor Laboratory. After the container was removed from the reactor, it was allowed to “cool” for one week to permit the decay of short-lived isotopes generated during the thermal neutron irradiation. The sections and the polycarbonate detectors were then removed and the detectors were placed in a solution of 5 M KOH at 70°C for 8-12 min with constant mild agitation. The detectors were then rinsed with filtered deionized water and allowed to dry. The plutonium fission fragments from the neutron irradiation create holes in the plastic detectors that appear as dark “tracks”. The sodium borate incorporated into the bone during the preparation step creates a subtle, latent bone image on the detectors through fission of the boron atoms. Selected bone sections used for NIAR were then mounted on plastic slides, polished and stained with a modified Giemsa stain for histological examination.

Analysis of autoradiographs

The algorithm proposed by Bruenger et al. (1991) was used for quantitative analysis of the NIARs. For this purpose, detectors were mounted on slides and every fourth viewing field was randomly selected (at magnification $\times 40$). All 8 viewing fields were photographed using a digital camera Olympus DP 11 (Olympus Optical Co, LTD, Japan) and micrographs were printed. The accompanying histological section permitted precise identification of the different structural elements of bone tissue and their boundaries on the autoradiograph. Endosteal surfaces, bone marrow, Haversian canal lumens and bone tissue of cortical and trabecular fractions were quantified. Trabecular bone fraction was observed in all 8 viewing fields, and cortical bone fraction was registered only in 2 viewing fields. Plutonium localization in bone tissue needs to be precisely determined for dosimetric calculations. It was assumed that the ‘ribbon’ outlining the interface of bone-marrow or bone-Haversian canal lumens relates to

endosteum area. For track calculation on endosteal surfaces, the width of this 'ribbon' was chosen corresponding to a plutonium fission track length. Based on previous data (Bruenger et al. 1991), this value was 18 μm , and according to data derived in this study a plutonium fission track length was 15 μm , as measured using a digitizing program (AxioVs40, v. 4.7; Carl Zeiss). Therefore, the 'ribbon' width specifying endosteum was chosen as 30 μm (15 μm on each side from interface) for calculation of plutonium fission tracks on endosteal surfaces (Fig. 1a-b, 2a-b). However, the observed histological endosteum width was much less. The width of the endosteum was measured in different areas of the histological section using the same digitizing program. The measured mean endosteum width was 6.2 μm (Table 2).

For identification purposes, the tracks were considered to be straight and not to exceed 20 μm in length (Fleischher et al. 1975). If a track crossed an interface (e.g., endosteum-marrow), it was assigned to the endosteum, since the probability of its location in endosteum area is much higher than in bone marrow (Lemberg et al. 1961; Bruenger et al. 1983; Polig et al. 1998). The authors scored the number of tracks in every structural element of bone tissue manually as well as areas and perimeters of these structures.

RESULTS AND DISCUSSION

According to the biokinetic model of the extrapulmonary compartment of the International Commission on Radiation Protection (ICRP 1994), there are cortical and trabecular fractions in skeleton, and each of these is subdivided into bone surfaces, bone volume and bone cavity compartment containing the bone marrow (Fig. 3). Results of plutonium fission fragment tracks scored in the different structural elements of bone tissue, areas of these regions on the sample and values of plutonium fission fragment tracks density in different structural elements are shown in Table 3. The data show that the plutonium distribution in bone tissue is very nonuniform, and this fact conforms to earlier animal studies (Lemberg et al. 1961; Bukhtoyarova and Nifatov 1969; Bruenger et al. 1983).

Limitations

There were some limitations in this study. First, there is little available data on potential plutonium wash-out from bone tissue fixed in neutral formalin. However, Tsedveleva's work (1960) contains a description of an experiment on rats, whose bone tissues during the part of experiments were processed twice with cold 5% trichloroacetic acid. Her work indicated a small portion of the plutonium was washed-out. Thus, if during the period immediately after radionuclide intake, procedures using powerful chemical reagents, there was an 8% wash-out of the nuclide fixed in the bone. It is reasonable to assume that in the case used in this study (Case #440), where the period between the date of plutonium contact and the date of death was more than 20 years, the plutonium was likely firmly fixed in bone tissue and long-term storage in formalin may not have resulted in significant wash-out. However, we cannot exclude the possibility that some translocation of the plutonium may have occurred during the storage period. This would need to be confirmed with an experimental study.

Another limitation is that when scoring, tracks crossing the interface of endosteum-marrow or endosteum-bone were classified as endosteum both for trabecular and for cortical bones, that results in a bias error.

The third challenge is accounting for the background content of natural uranium in the human skeleton. Because uranium is also fissionable, as is plutonium, it can produce fission fragment tracks on autoradiographs that are indistinguishable from the plutonium tracks. The impact of natural uranium content on the quantification of plutonium in bone can be estimated using the neutron physics of these isotopes. Using the analysis outlined in Krahenbuhl and Slaughter (1998) the ratio of fission events due to target nuclei (^{239}Pu) to total fission events can be

mathematically determined. Nuclear reactions are first-order irreversible reactions. In the irradiation process, the following competing fission reactions are taking place:

Each reaction rate is described by eqn (1):

$$v = N\phi, \quad (1)$$

where v is reaction rate in interactions ($\text{cm}^{-3} \text{s}^{-1}$), ϕ is neutron-flux density (neutron $\text{cm}^{-2} \text{s}^{-1}$), N is atom density (atom cm^{-3}) and σ is microscopic cross-section (barn). For fission processing system with competing first order reactions the overall reaction rate is given here in eqn (2):

$$v = \sum_i N_i \sigma_i \Phi. \quad (2)$$

The concentration of neutrons is several orders of magnitude greater than that of the fissile atoms; thus, we assume constant flux for all species. After some algebraic manipulation the ratio of fission events due to ${}^{239}\text{Pu}$ to total fission events is given below in eqn (3):

$$K_{239\text{Pu}} = \frac{N_{239\text{Pu}} \sigma_{239\text{Pu}}}{\sum N_i \sigma_i} \quad (3)$$

The concentration of ${}^{238}\text{U}$ in human bone tissue is within the range of 100-200 mBq kg^{-1} (Moiseev and Ivanov 1990), for people residing in regions with normal natural radiation background (predominantly as a result of entering through the digestive tract). Average concentration of ${}^{238}\text{U}$ in cortical and trabecular bones on averaged data of United Nations Scientific Committee on the Effects of Atomic Radiation is 150 kBq kg^{-1} (UNO 1982). On the basis of the ratio ${}^{238}\text{U}$ and ${}^{235}\text{U}$ in isotopic composition of natural uranium, averaged concentration of ${}^{235}\text{U}$ in human bone tissue is 1.08 kBq kg^{-1} .

The content of ${}^{239}\text{Pu}$ in the skeleton for case #440 was determined to be 20 kBq . Considering that the skeleton mass of adult man is estimated to be about 10.5 kg (ICRP 2003), then the content of ${}^{239}\text{Pu}$ per kilogram of bone tissue for our case was 1.9 kBq kg^{-1} .

Knowing the content of isotopes in the sample as well as their microscopic cross-section on thermal neutrons, it is possible to find the ratio of fission events due to ${}^{239}\text{Pu}$, ${}^{235}\text{U}$ and ${}^{238}\text{U}$ to total fission events from eqn (3). Results of calculations are presented in Table 4. As can be seen from the table, the fission events due to ${}^{239}\text{Pu}$ outnumber all other combined fission events. Thus, the contribution of natural uranium content on the number of fission tracks is negligible and most of the tracks are the result of ${}^{239}\text{Pu}$ fission events.

Testing of ICRP model

For the purposes of dosimetry, the bone cavity compartment is assumed to consist entirely of bone marrow in cortical and trabecular fractions (ICRP 1994). However, bone marrow in the cortical fraction is essentially non-existent when evaluated using histological criteria (Ham and Kormak 1983). Haversian canals exist in mature cortical bone and were observed in the

cortical bone in this study (Fig 2a). The Haversian canal is also lined with endosteal-like tissues, but the tracks arising from the Haversian surfaces were assigned to the cortical surface compartment.

The data derived from this study were tested against the biokinetic model recommended by the ICRP for assurance of radiation protection standards. The authors considered the ratio between track number in bone volume and track number on bone surface for cortical and trabecular fractions – $q(CV)/q(CS)$ and $q(TV)/q(TS)$, correspondingly.

Using values of volume and surface of bone tissue for cortical and trabecular fractions of the reference man skeleton (Table 5), the authors approximated the data derived from one slide (Table 3) to the whole skeleton. At the same time, for determination of an elementary volume of bone tissue, in which tracks of fission fragments were scored, the area of track scoring was multiplied by the track length (15 μm), except for the endosteum areas (where it was multiplied by the actual endosteum width in the relevant area). Actual values of these parameters for cortical and trabecular fractions were 2.0 and 0.4, correspondingly. These ratios were calculated for this case at the time of death for two scenarios of intake: acute (intake in the first working day) and chronic (uniform intake over the time of contact with radionuclide) using IMBA Professional Plus program, v. 4.0. Calculated and actual values of the ratios between number of decays in the bone volume and number of decays on the bone surface are presented in Table 6. As can be seen from the table, values of parameters coincide for trabecular bone but significantly differ for cortical bone.

It should be noted that track density on bone surfaces is an order of magnitude greater than in bone volume for cortical and trabecular fractions according to scoring data of plutonium fission fragment tracks.

Plutonium is initially deposited on bone surfaces but becomes buried and redistributed with time (Miller et al. 2003). Thus the heavy surface concentrations of ^{239}Pu in the NIAR from the worker would suggest a more recent deposition. There are several possible explanations for this. One is that this worker had a very substantial plutonium exposure shortly before death. This was not considered likely considering the employment history of this worker. Another explanation is that plutonium that is recently resorbed and released during bone remodeling may also redeposit onto bone surfaces, as observed in experimental studies (Priest and Giannola 1980). In this regard, ^{241}Am was observed on vertebral cancellous bone surfaces 11 years after exposure in a human case (Priest et al. 1995). Another explanation is that there was a late in life translocation of ^{239}Pu from the liver. The liver is the other major deposit of plutonium in the body and data from the RHRTR indicates that in workers with a normal health status and from 2-4 decades after their plutonium exposures, the liver contains about 42% of the total residual amount of plutonium in the body with about 50% in the skeleton (Suslova et al. 2002). However, when the late-in-life health of the individual is considered, recent data shows that with diseases that affect the liver (such as hepatitis, cirrhosis, metastatic disease or other degenerative diseases), there is a release of plutonium from the liver, some (or perhaps even most) of which appears to be incorporated into the skeleton (Suslova et al. 2003). In several studies on the concentrations of plutonium from fallout in humans, the presence of chronic or acute diseases that affect the liver was reported to result in a decreased retention of plutonium in the liver relative to other organs (Mussalo et al. 1980; Griffith and Guilmette 1991). In the present study, the worker died from a pulmonary cancer with metastatic disease that involved the liver and this may account for some, or perhaps most of relative deposition of ^{239}Pu on bone surfaces for this individual.

Moreover, plutonium burden in bone volume is considerably greater than plutonium burden on bone surfaces (Table 6). The data indicates a considerable underestimation of resorption

from bone surfaces to bone volume for cortical fraction. It should be noted that these data are preliminary, and they require further development based on of different types of bones and on other cases.

CONCLUSIONS

1. Quantitative data for plutonium microdistribution in human bone tissue was obtained for the first time on an sample of a thoracic vertebra specimen;
2. Plutonium distribution in this specimen was very non-uniform. The track density on endosteal surfaces is the next-higher order of magnitude than in the volume of bone tissue, both in cortical and in trabecular fractions;
3. Actual ratio between the number of ^{239}Pu decays in bone volume and number of ^{239}Pu decays on the bone surface does not coincide with the ICRP recommended values for cortical bone;
4. It is possible that biokinetic model parameters of extrapulmonary ICRP compartment might need to be adjusted following further studies on quantitative plutonium microdistribution in other human bone types and in individuals with different exposure patterns and scenarios.

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Fig. 1. Structural elements of trabecular bone in (a) histological image, and (b) neutron-induced autoradiograph. M, Marrow; ES, endosteal surface; BV, bone volume. x40.

Fig. 2. Structural elements of cortical bone (a) histological image, and (b) neutron-induced autoradiograph. ES, endosteal surface; BV, bone volume; EH, endosteum of Haversian canals; lumen of Haversian canal is indicated by an arrow. x40.

Fig. 3.
Diagram of the skeletal ICRP model for plutonium (ICRP 1994).

Figure 4.

Figure 5.

Table 1

Characteristics of RHRTR case #440.

Criteria	Characteristic
Gender	Male
Plutonium working period	13.5 y
Period between end of plutonium contact and death	25.5 y
Age at death	64 y
Cause of death	Lung cancer
Liver pathology	Metastases of papillary adenocarcinoma Nidal adipose degeneration of hepatocytes
Plutonium skeletal content	20 kBq
Plutonium liver content	6.5 kBq
Plutonium lung content	0.4 kBq
Plutonium body burden	44 kBq

Table 2

Endosteum width in different compartments of the vertebral specimen.

Bone tissue compartment	Endosteum width, μm
Endosteum of trabecular bones	4.9 (95%CI=4.1 - 5.7)
Endosteum of cortical bone surface	5.8 (95%CI=5.0 - 6.6)
Endosteum of Haversian canals	7.2 (95%CI=5.9 - 8.5)

Table 3

Number and density of ²³⁹Pu fission fragment tracks in different parts of the bone tissue.

Bone type	Compartment	Tracks, number in compartment	Surface of area of tracks calculation, × 10 ⁻⁷ m ²	Track density, × 10 ⁷ tracks m ⁻²
Cortical	Bone volume	6,283	25.1	250
	Cavities of Haversian canals	29	0.4	73
	Endosteum	985	0.3	
	Endosteum of Haversian canals	415	0.2	2,800
Trabecular	Bone volume	10,165	25.7	396
	Bone surface (Endosteum)	9,955	2.8	3,555
	Bone marrow	2,728	215.2	12.7

Table 4

Calculated ratios between fission events from ^{239}Pu , ^{235}U and ^{238}U , and all fission events in the bone sample.

Parameter	Isotope		
	^{239}Pu	^{238}U	^{235}U
Plutonium burden per 1 kg of bone tissue, Bq kg ⁻¹	1.9×10^3	1.5×10^{-5}	1.08×10^{-3}
σ_i , barn	7.5×10^2	5.0×10^{-6}	5.85×10^2
N_i , nuclei/kg	2.14×10^{15}	3.06×10^{16}	3.47×10^{13}
$K_i = N_i \sigma_i / \sum N_i \sigma_i$	9.88×10^{-1}	9.38×10^{-8}	1.25×1

Table 5

Values of volume and surface of bone tissue for cortical and trabecular fractions of the skeleton in Standard Man (ICRP 2003).

Bone type	Parameter	
	Bone tissue volume, cm ³	Bone tissue surface, m ²
Cortical	2,130	6.5
Trabecular	580	10.5

Table 6

Actual and calculated values of ratio between decay number in bone volume and decay number on bone surface for cortical and trabecular fractions.

Parameter	Actual value	<u>Scenario of intake</u>	
		Acute	Chronic
$q(\text{CV})/q(\text{CS})$	2.0	0.4	0.3
$q(\text{TV})/q(\text{TS})$	0.4	0.6	0.6