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A PHYSIOLOGICAL SKELETAL MODEL FOR RADIONUCLIDE AND STABLE ELEMENT BIOKINETICS IN CHILDREN AND ADULTS

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A PHYSIOLOGICAL SKELETAL MODEL FOR RADIONUCLIDE AND STABLE ELEMENT BIOKINETICS IN CHILDREN AND ADULTS

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Abstract –

A physiological skeletal model (PSM) is described that represents the skeletal uptake, retention and clearance of both bone-surface-seeking and bone-volume-seeking radionuclides and stable elements. A key objective of the PSM is to model the higher skeletal growth and bone turnover in infants and children (compared to adults) in order to to account for their greater uptake and cancer risk from bone-seeking contaminants such as lead and plutonium. The PSM is a compartmental model that allows for the incorporation of organic and inorganic material in the bone volume via quiescent bone surfaces, forming bone surfaces and the lacuno-canaliculi system. The model uniquely incorporates a tertiary phase of mineralization via bone fluids. The PSM's structural concepts and biokinetic parameters - such as realistic mass transfers, organ and tissue masses, and bone remodelling half times - are selected mainly on the basis of physiological and anatomical criteria. For brevity, model parameter values or evaluated for adults only. The PSM is an improvement on existing skeletal models that are based more on compartment structures and pathways that rendered good fits to biokinetic data rather than on being anatomically and physiologically accurate.

Keywords: Bone, dose, internal; dose assessment; intake, radionuclide.

INTRODUCTION

Compartmental biokinetic elemental skeletal models by Leggett (1985; 1992) were adopted and modified by the International Commission on Radiological Protection (ICRP 1993; ICRP 1995b) in order to better describe the uptake, retention and release of radionuclides within the skeleton. There are two forms of generic elemental skeletal models in use by the ICRP. The first is a model for "calcium-like" or "bone-volume-seeking" elements including lead (Pb), uranium (uranyl ion UO_2^{2+}) and the four following alkaline earth elements: calcium (Ca), strontium (Sr), barium (Ba) and radium (Ra). The second is a model for "plutonium-like" or "bone-surface-seeking" elements such as thorium (Th), neptunium (Np), plutonium (Pu), americium (Am) and curium (Cm). A similar surface-seeking model is proposed for lanthanides by Taylor and Leggett (2003), but for brevity is not considered further. The names 'Ca-like' for volume-seeking elements and 'Pu-like' for surface-seeking elements shall henceforth be used for convenience. A compartmental name, 'Quiescent Volumes' (in the plural), refers to the two following bone compartments: Trabecular Quiescent Volume and Cortical Quiescent Volume.

The aim of this paper is to develop the conceptual structure of a generic skeletal model – based on physiological processes – that accurately represents the biokinetics of radionuclides and stable elements. The biokinetic behaviour of elements and compounds within the skeleton is

mainly due to their competitive uptake by, and biochemical interactions with, various forms of bone surface as well as their transport in bone fluid by diffusion and convection processes. Although there are dissimilarities between the ICRP skeletal models for 'Ca-like' and 'Pu-like' elements, any specific characteristic of these two generic models is exhibited by all bone-seeking elements, but to different extents. For example, Leggett (2003) proposed a new Pu model that has material from blood not only deposited in a compartment for bone surface, but also transported to bone volume (a characteristic of Ca-like models) to depict rapid burial of Pu during bone formation. An illustration of a Ca-like element with diverse biokinetic characteristics is provided by Priest et al. (1982), who showed that uranium is initially deposited on both quiescent and forming bone surfaces, with a preference for the latter. Accordingly, the ICRP treats uranium as a volume-seeking radionuclide typified by the alkaline earth elements. However, uranium also shares characteristics in common with other actinides, including a propensity to bind to plasma proteins.

Richardson et al. (2007) and Nie and Richardson (2009), using Monte Carlo simulations, evaluated the radiation dose to the skeleton for alpha and beta emitters incorporated in new bone during bone remodelling. The latter study hypothesized that radiation-induced bone cancers are more likely to occur in close proximity to bone remodelling (i.e., forming bone) due to the elevated radiation damage to stem and progenitor cells in these highly vasculated, well oxygenated and hence radiation-sensitive locations. The partitioning of the peripheral marrow into two radiation 'targets' adjacent to forming and quiescent bone surfaces is particularly relevant for non-adults, for whom bone growth is an important predisposing factor associated with both spontaneous and radiogenic bone cancer.

A generic physiological skeletal model (PSM) was designed to assess the toxicity of contaminants in adults, children, infants, and perhaps the third trimester fetus. It accommodates the major physiological processes of both the Ca-like and Pu-like bone-seeking elements. The intention is that the PSM can be simplified and the nominal parameters modified to match the biokinetics of a specific radionuclide or elemental intake. One objective of the PSM is to model the biokinetics of radionuclides and stable elements in anatomical locations within, or in close proximity to, target areas in the skeleton that if irradiated have the potential of inducing bone cancer or leukaemia (Richardson, In press). This objective is particularly important in order to accurately assess the greater vulnerability of non-adults to the internal radiation exposure from bone-seeking radionuclides. For example, it is estimated that for infants compared to adults the overall average cancer mortality risk per unit activity of selected inhaled radionuclides and ingested radionuclides is 10 times higher and 100 times higher, respectively (Richardson 2009a).

About one-third of the dry mass of bone consists of an organic matrix that is mainly collagen (a protein); while the remaining two-thirds is comprised of inorganic calcium hydroxyapatite, a crystallized calcium phosphate salt. The PSM was designed to facilitate the biokinetic modelling of radionuclides or stable elements that can be in the form of both organic and inorganic molecules or compounds in the skeleton. This feature is not only needed for modelling tritium and ^{14}C (e.g., in hydrocarbons and tritiated water/bicarbonate), but also for modelling many Ca-like and Pu-like elements as they exist in both organic and inorganic forms in the body. The two ICRP generic elemental skeletal models are analysed to identify the compartmental structure and parameter values that are either beneficial or limiting to a single novel skeletal model that encompasses the characteristics of both the Ca-like and Pu-like models (ICRP 1993; ICRP 1995b). It is recognized that PSM parameter values will depend on the specific radionuclide or stable element being modelled. In this paper the general concepts of the

PSM are described (and nominal parameter values selected) for adults and enumerated in terms of the physiological nature of the compartments, their masses and their pathway transport times.

ICRP's BONE-VOLUME- AND BONE-SURFACE-SEEKING MODELS

General characteristics

The biokinetic compartmental characteristics of the ICRP skeletal models for volume-seeking and surface-seeking elements are analysed as part of the process to create a PSM (ICRP 1993; ICRP 1995b). The compartment half times given in Tables 1 and 2 for six bone volume-seeking and five bone surface-seeking elements are calculated based on rate constant data recommended by the ICRP for adults. A half time is equal to ln(2) divided by the rate constant. The range of pathway half-times for the ICRP generic skeletal models are shown in Figs. 1 and 2. The general structural concepts that apply to both the Ca-like and Pu-like models are as follows. First, uptake from blood plasma to the skeleton is solely via bone surfaces. Second, material from the bone surface and bone volume is either moved back to plasma/blood or transported to trabecular marrow and cortical cavities. Third, resorption of material from the trabecular and cortical bone volume back to plasma/blood (adult half times of 3.9 and 23 years, respectively) is element independent and related to the age-specific bone turnover rate. Fourth, the ICRP models for Pu-like elements have a single compartment representing whole blood. However, for Ca-like elements two compartments are allocated to whole blood, one representing activity bound to red blood cells and a separate compartment for activity in plasma. In general, Ca-like elements mainly exist in blood as either plasma ions or bound to red blood cells. For example, >99% of the Pb activity in whole blood is bound to red blood cells (ICRP 1993). Conversely, Pu-like elements mostly bind to plasma proteins: little of the activity present in whole blood is associated with red blood cells (≤10%), with the notable exception of Th^{4+} (Lloyd et al, 1984; Durbin 2006)

Structural concepts and parameter values specifically relevant to each generic model are as follows. First, all Ca-like and some Pu-like elemental models have slightly faster (~1.25-fold) uptake from plasma/blood to trabecular bone compared to cortical bone. The exceptions are for the surface-seeker, Pu, for which the trabecular:cortical ratio is 1.5 and for Th, Am and Cm, where the half-times are equal. Second, the bone volume is a single compartment for Pu-like elements, but split into two parts for Ca-like elements. Third, the ICRP (1995a) now assigns 60% and 40% of the adult skeletal bone surface to trabecular and cortical bone, respectively.

Bone-volume-seekers

The initial uptake of the six bone volume seekers – Ca, Sr, Ba, Ra, Pb and U (solely as UO_2^{2+}) – from plasma to bone surfaces is relatively rapid with a half time of ≤10h (Table 1, Fig.1). Only one-sixth of the rapidly deposited bone surface activity passes to the exchangeable bone volume, while five-sixth is returned to plasma, with a half time of 1.2 h for four of the six Ca-like elements (ICRP 1993, ICRP 1995b). The exceptions are outliers Pb (half time, 1.4d) and U (10d), where the activity transferred from bone surface to bone volume and plasma is equal.

Volume-seeking models have their bone volume divided into two sub-compartments. Uptake from plasma passes first to the shallow or exchangeable bone volume, then to the deep or non-exchangeable bone volume of mature bone. In ICRP Ca-like models between 40% (i.e. Ca) and 80% (i.e. Ra, Pb) of an element migrates from exchangeable to non-exchangeable bone volume. Leggett (1992) considered an alkaline earth element's fractional transfer from shallow bone volume to deep bone volume to depend on its discrimination to permanently or temporarily

bind to bone crystal (see Bone Fluid compartments section). The activity of the exchangeable volume compartment is associated with free ions in bone fluid which are found both in the canaliculi and in the hydration shell surrounding bone mineral crystals (Pollack 2001). The activity of the non-exchangeable volume is associated with 'bound water' that has a longer retention period than the exchangeable volume due to the strong binding of activity to the bone mineral, hydroxyapatite crystals.

Bone-surface-seekers

The rate of uptake from blood to bone surfaces is the only difference in the adult pathway rate constants of the ICRP bone surface-seeking models for the five Pu-like elements,–Th, Np, Pu, Am and Cm (Table 2, Fig. 2). All other pathway rate constants are the same; this implies a similarity in the manner in which these actinides are transferred into and out of the bone volume. The processes that transport material into bone volume can involve bone fluid, bone remodeling or to a lesser extent, diffusion via quiescent bone surfaces (see the Physiological skeletal model section). The Pu-like bone volume is represented as a single compartment equivalent to the combined non-exchangeable and exchangeable bone volumes of Ca-like elements. Pu-like elements display less evidence than Ca-like elements of diffusive or convective transport in bone fluid, hence less need for a separate exchangeable bone volume compartment. The activity binding to bone surface is strong, as transport of Pu-like activity to bone volume is extremely slow: the rate constant for clearance from bone surface is half that of bone volume resorption. Activity is lost from bone volume to trabecular marrow or cortical (Haversian) cavities at the bone volume turnover rates (e.g., 23 y for cortical bone), perhaps implying that surface-seekers are released from bone volume only when resorption occurs. There is a delay ($T_{1/2}$ ~90 d) in the clearance of activity residing in trabecular marrow or cortical cavities before it is released to blood; this delay accommodates the uptake and subsequent release of radionuclides within scavenging macrophages.

PHYSIOLOGICAL SKELETAL MODEL

The PSM reproduces many of the pathways found in the ICRP bone-volume and bone-surface seeking models (Fig. 3). There are five additional criteria compared to the ICRP models for determining the PSM's biokinetic behaviour (see Discussion for supporting research). First, each compartment represents a physiological entity in composition, pool mass and material transport; this is not always the case with the ICRP Ca-like and Pu-like bone models. For example, although a mass was assigned to the trabecular and cortical surface compartments in ICRP Publication 30 (1979), an infinitely thin source was employed in the evaluation of associated dosimetric parameters (Cristy and Eckerman 1993). Second, the PSM was developed so that account can be taken of the inorganic and organic radionuclide/stable compounds (that largely parallels ionic and non-ionized species) in blood and the skeleton. Third, the fractional deposition of the skeletal uptake material is separated into material going to new bone, bone fluid, quiescent bone surfaces and forming/remodelling bone surfaces. Fourth, biokinetic pathways accommodate the movement of material from forming bone surfaces to either new bone or back to plasma. Fifth, similar to Leggett's (1992) exchangeable volume compartments, the activity in the PSM's bone fluid and forming surface compartments turns over relatively rapidly, resulting in well-mixed compartments in exchange with blood plasma.

The PSM has pathways transferring inorganic and organic material from the Plasma compartment (apart from Bone Fluids) to Quiescent Surfaces and Forming Surfaces that together represent: a) the trabecular bone surfaces of the marrow cavities, namely the endosteum, and b) the cortical bone surfaces of the Haversian and Volkmann canals. Some of the material (one-sixth in the ICRP Ca-like models) taken up from plasma by the Forming Surface compartment is transferred relatively rapidly to New Bone, supplemented by more inorganic mineralizing material from Plasma.

Organic and Inorganic Species in Blood

One reason for the development of this new skeletal model is to accommodate the dissimilar characteristics of both the inorganic species (including elemental ions) and the organic species found in the intra- and extra-vascular spaces. Accordingly, the PSM has both Organic Plasma and Inorganic Plasma compartments. The ICRP's normal practice is to accord one elemental dosimetric model to each radionuclide no matter the nature of the intake compound containing the radionuclide (see Discussion). However, for radionuclides or elements that are strongly bound within organic compounds, their biokinetic behaviour depends on the carrier compound. The ICRP recognizes this to be the case for hydrogen (i.e., tritium), carbon, sulphur, and iodine elements, for which several different compound models are recommended. For example, there is a marked variation in the biokinetics of tritium bound to water and organic compounds found in food (Richardson and Dunford 2003) including differing skeletal biokinetics that can be addressed by the PSM.

ICRP (1993) incorporates a red blood cell compartment within plasma for only Ca-like elements (Fig. 1), while the PSM includes a red blood cell compartment for use with both Ca-like and Pu-like elements (not shown in Fig. 3). Experimental evidence shows Pu, Am, Cm and Cf, depending on their valency, exist in oxidation states where >90% of these elements in blood are found in plasma (Taylor 1998). However, the greater part (≥70%) of Pb, U, and the Pu-like element Th, is bound to blood cells. The bone surface activity of Ca-like models is dominated by rapidly exchangeable activity associated with relatively small positive ions, whereas most Pu-like elements are primarily bound to plasma proteins. For example, slightly more than half of plasma Ca is in ionic form and readily exchangeable with extra-vascular Ca, while the rest is bound to proteins such as albumin and is not diffusible (Borle et al.1981).

Both Ca-like and Pu-like radionuclides and stable elements bind to citrates (salts of a weak organic acid) in physiological pH conditions. Calcium creates the smallest ion complex and among the Ca-like elements has the greatest fraction binding to citrates (15%), followed by Sr, then Ba, with only 0.4% of circulating Ra being bound to citrate. The metal ions of both Ca-like and Pu-like elements have a tendency to form aqua ions which can hydrolyze, especially in aqueous media such as blood plasma. The formation of stable complexes with plasma proteins, such as transferrin and albumin, is a competitive reaction to hydrolysis (Taylor 1998). All Pu-like elements bind strongly to plasma proteins, except for outliers Am and Cm that bind weakly and have blood clearance half times within the range of Ca-like elements. Uranium is modeled by the ICRP as a Ca-like element. However, uranium is an actinide that generally exists as a uranyl ion, UO_2^{2+}. Although bicarbonate is the dominant ligand in body fluids, about 30-40% of circulating UO_2^{2+} is bound to transferrin, a glycoprotein that binds to iron and plays an important role in erythropoiesis and mitosis, especially in bone marrow (Durbin 2006). Albumin, which accounts for 60% of serum protein, is incorporated into the calcified matrix during bone formation. Chipperfield and Taylor (1972) found that actinides bind to glycoprotein fractions

isolated from bovine cortical bone in the order Th > Pu > (Am = Cm); this preference for binding by actinides may also apply to serum proteins incorporated into the non-mineralized portion of bone deposits on quiescent and forming bone surfaces. In sum, there is considerable overlap of the skeletal biokinetic characteristics of Ca-like and Pu-like elements that the PSM is designed to accommodate.

Quiescent Surface Compartments

Most of the bone surface of an adult can be assumed to exist in a quiescent state, i.e., ~94.0% and 97.6% of the total trabecular and cortical bone surface, respectively (Table 3), based on ICRP (1995a) values modified by the measurements of Jowsey et al. (1965). According to Cristy and Eckerman (1993) radionuclides that bind to quiescent bone surfaces can be represented as an infinitely thin radiation source. However, organic and inorganic material may be deposited on bone surfaces in adjacent finite layers as both the forming and quiescent bone surfaces are covered by a layer of un-mineralized organic material (Chow and Chambers 1992) that forms an approximately 1 μm thick 'endosteal membrane' (Parfitt 1984). A finite thickness of 1 μm for activity deposited on bone surfaces has been allowed for in the PSM Quiescent Surface compartments, as this is a significant factor in the dosimetry of very short-range particles such as tritium (Richardson et al. 2007). Autoradiography carried out by Riggs et al. (1971) showed that rapidly exchangeable (inorganic) Ca was located within 1 μm of the mature bone surface of adults. In individuals exposed more than 25 years earlier, Schlenker and Oltman (1986) measured high alpha-particle concentrations that extended from the endosteal cortical bone surfaces to depths of 2.0-4.3 μm and 0.6 μm for ^{226}Ra and ^{241}Am, respectively. Therefore, experimental evidence showed that radionuclides were passively transported only a short distance when deposited on quiescent bone surfaces. Accordingly, in the PSM the movement of material along the compartmental pathway from the quiescent bone surface to bone volume (unlike the ICRP Pu-like models) was negligible, and the pathway superfluous, compared to the substantial amount of material incorporated into the bone volume via bone fluid and bone remodelling.

Forming Surface and New Bone Compartments

New bone in the form of hemiosteons in trabecular bone and osteons or Haversian systems in cortical bone are both the products of remodelling. This remodelling occurs at forming surfaces, which comprise only 5% and 2% of the PSM's total bone surface within adult trabecular and cortical bone cavities, respectively (Table 3). Both Ca-like and Pu-like elements (such as Ca and Pu) may be found 'buried' in newly formed bone as the result of bone remodelling (Marshall 1962; Priest and Hunt 1979). The Forming Surface compartment exchanges activity with Plasma; the Forming Surface also passes on organic and inorganic material on to New Bone. All activity in New Bone eventually feeds into the Quiescent Volume compartment. The employment of Forming Surface and New Bone compartments in the PSM will allow radionuclide burial to be accounted for in dosimetric Monte Carlo simulations (Richardson and Nie 2009).

Osteoclastic resorption, mononuclear cell resorption and the reversal phase occur in about 51 days in trabecular bone (Jee 2001). Matrix synthesis takes place for ~15 days before the initial rapid linear increase in mineralisation (Eriksen 1984). The osteoid seam reaches 70% of the terminal mineralisation (100%) during the primary mineralization process in 5 to 10 d (Jee 2001). This is followed by secondary mineralisation, with the primary and secondary

mineralisation together occuring in about 130 d in trabecular bone (Eriksen 1984). A slower 'tertiary or terminal' phase of mineralization is hypothesized and accommodated in the PSM (see Discussion). The duration of cortical bone mineralisation was considered by Parfitt (1983) to be ~1.4 fold longer than that of trabecular bone. The PSM's cortical bone, compared to trabecular bone, has a greater percentage of its minerals taken up via bone fluids during the tertiary mineralization phase due to the longer duration in cortical bone before remodelling occurs.

The PSM's Forming Surface compartment represents an osteoid layer, mainly composed of collagen and organophosphate proteins, which then undergoes primary mineralisation. The uptake and clearance half time of organic and inorganic material by the Trabecular and Cortical Forming Surface compartments are assumed to be 3.7 and 2.3d, respectively (roughly a fifth of the time for matrix synthesis and initial mineralization). The amount of material moving from plasma to the cortical forming surface is ~1.5-fold less that of the equivalent trabecular compartment.

It is within 'New Bone' where the slower secondary phase of mineralisation takes place from 70% to ~98% of the terminal mineralisation in trabecular bone (and 70% to ~90% in cortical bone) in a non-linear fashion i.e., two-thirds at the mid-time of this phase (Hernandez et al. 2001). In the PSM the terminal minerals are transported to the Quiescent Volumes via the Bone Fluid compartments. The nominal clearance half times of the Trabecular and Cortical New Bone compartments are estimated as about a third of the secondary mineralisation phase, i.e., 45d. The average mineralisation mass of the Trabecular Forming Surface compartment is 0.18, as a fraction of the total bone mass (Table 3). This is midway between the 0.03 mineral mass fraction found in collagen and 70% of the terminal trabecular bone mineral mass fraction of 0.50 when the primary mineralisation is complete. The composition and mineral content of the other PSM compartments are evaluated in a similar manner.

An unmineralized, organic osteoid seam is about 15-16 μm thick during the initial bone formation period, but then rapidly decreases in thickness, becoming calcified to form a lamella (Eriksen 1984). The masses of the Trabecular and Cortical Forming Surface compartments given in Table 3 represent an average lamellar thickness of 3 and 5 μm, respectively (Kragstrup et al. 1983; Parfitt 1983). In order to limit the complexity of the PSM, the Forming Surface compartments do not include osteoblasts that bring in Ca^{2+} for mineralisation, even though these cells have up to 13-fold the concentration of Ca^{2+} compared to soft tissue cells (Imai et al. 1992).

Quiescent Volume Compartments

The Quiescent Volume compartments of adult trabecular and cortical bone have half times of 3.9 and 23 years, respectively (ICRP 1995a). The Quiescent Volumes comprise the major part of the trabecular and cortical bone masses of 1.1 and 4.4 kg, respectively. Separate compartments for the resorbing surface are not adopted, as they occupy only about a fifth of the trabecular and cortical bone surface area. In principle, compartments for resorbing surfaces that represent activity in macrophages, monocytes and osteoclausts could be allocated a portion of the activity in the PSM's Trabecular Marrow and Cortical Cavities compartments (see section below of the same title).

Bone Fluid Compartments

Water, oxygen, glucose, amino acids and Ca ions are small molecules or atoms that are transported into the bone volume via bone fluid, probably within minutes, by bulk flow (due to mechanical loading) and diffusion (Knothe Tate 2001). Nutrient transport is from the interstitial

fluid in bone marrow sinusoids – these sinusoids are either within the trabecular cavities or the Haversian and the Volkmann canals – along the lacuno-canaliculi system to osteocyte cells. Likewise, waste products leave bone via the lacuno-canaliculi system. The relatively small ions of alkaline earths, a volume-seeking material, find their way by diffusion and convection to all bone surfaces, including those lining the canaliculi and lacunae (Marshall and Onkelinx 1966). Diffuse ^{45}Ca activity in the bone volume, half an hour after administration, was a twentieth that of the maximum hotspots in forming bone including those in periosteum (Cohen and Maletskos 1962). The mass transport of relatively large organic molecules, such as albumin of molecular weight 64,000-69,000, is more slowly achieved by strain-derived flow in bone fluids.

The lacuno-canaliculi system is found in trabecular and cortical bone wherever there are osteocytes. Robinson (1964) estimated the surface area of the skeletal Haversian and Volkmann canals lacunae and canaliculi to be 2-3 m^2, 43 m^2 and 651-1085 m^2, respectively. Marotti et al. (1995) measured the canaliculi density in cortical bone as 5.5 canaliculi openings on 100 μm^2 of Haversian surface. If the canaliculi were in parallel and equidistant from each other, they would be on average about 4.3 μm apart. Therefore, about 30% of the bone volume is perfused assuming a diffusion distance of 1 μm radiating from parallel canaliculi of radius 0.1 μm. This large passive diffusion volume (presumably found in free water) is characteristic of a volume-seeking material such as an alkaline earth ion (Marshall and Onkelinx 1966).

Some activity in the PSM's Bone Fluid compartments feed into the Quiescent Volumes, except for that activity returning to Plasma (Fig. 3). The osteocyte/lacunae density is similar in human trabecular and cortical bone (Sissons and O'Connor 1977; Mullender et al.1996). Therefore the PSM clearance half times for the bone fluid pathways are the same for these two bone types. The mass of both Bone Fluid compartments is based on Eriksson's (1976) estimate that free water is 2% of bone mass, or 3.9% by volume (Table 3). This bone fluid mass is about midway among Pollack's (2001) collected range of values. The PSM's bone fluid flow rate is assumed to be 600 $\mu l\ g^{-1}\ h^{-1}$ (Knothe Tate 2001), which leads to biokinetic uptake of material in the bone volume from the bone fluid flow similar to that seen for albumin and calcium in animals and humans (Groer and Marshall 1973; Owen and Triffitt 1976). The Ca concentration in bone fluids is about two-thirds that found in plasma (~100 mg L^{-1}): it is assumed that two-thirds of the Ca flow in bone fluids provides the tertiary-phase minerals to the quiescent volume bone (Neuman and Ramp 1971; Green and Kleeman 1991). These assumptions lead to bone fluids supplying 1.9 and 9.6% of the terminal bone mineral level of the trabecular and cortical quiescent bone volumes, respectively, when allowance is made for 62.5% of the bone mineral mass being other than Ca (ICRP 1995a).

Bone Fluid clearance half times 0.8 and 1.7 d are shown in Fig. 3. In practise the PSM clearance times (like those of the ICRP models) for radionuclides leaving the bone's exchangeable (bone fluid) volume for the non-exchangeable (quiescent bone) volume will depend on the actual element or compound being modeled (ICRP 1993; ICRP 1995b; Table 1). For example, Leggett (1992) notes that the likelihood of activity in blood reaching a non-exchangeable site in bone crystal via forming bone, and presumably also via bone fluid, decreases in the order Ca > Sr > Ba > Ra.

Trabecular Marrow and Cortical Cavities Compartments

The PSM and the ICRP skeletal models for Pu-like elements (unlike Ca-like models) both contain compartments for trabecular marrow and cortical cavities, the latter including Haversian canals. This is because colloid-bound Pu-like activity is recognized as waste

by the body and initially taken up by osteoclasts engaged in remodelling then engulfed by macrophages located in marrow, with higher concentrations of contaminated macrophages close to bone surfaces (Bleaney 1969; Priest and Giannola 1980). Activity in the ICRP or PSM's trabecular marrow and cortical cavities is assumed to clear to plasma with a half time of 90d (Leggett 1985). There is an additional benefit to the inclusion of Trabecular Marrow and Cortical Cavities compartments in the PSM. Dose estimates for the endosteum and other marrow 'targets' associated with radiation-induced cancer, can be greatly improved by accounting for the differential retention/solubility in haematopoietic tissue and fat cells associated with particular elements such as radon (16-fold) and plutonium (up to 30-fold) (Leggett 1985; Richardson et al. 1991).

DISCUSSION

The need for two forms of carrier species in blood being accommodated in the potential use of the PSM may not be limited to organic and inorganic hydrogen, carbon, sulphur and iodine. There is experimental evidence that the chemical form of injected Pu influences its distribution in blood, soft tissues and the skeleton due to differences in systemic and hepatic transport (Fouillit et al. 2004). Recently, Schimmelpfeng (2009) published a physiological pharmacokinetic model for the biokinetics of Pu in the body, which includes separate compartments (that interact with different organs) for Pu bound to citrate and transferrin, both found in blood plasma and interstitial fluid. Albeit, when assessing the radiation dose to the body using current ICRP compartmental models for intakes of Ca-like and Pu-like radionuclides, the ICRP assumes that their biokinetic behaviour in blood, soft tissues and the skeleton is independent of the species of uptake.

The PSM was developed primarily to accommodate the physiology and skeletal tissues that in fetuses, infants and children exhibit greater vulnerability to radionuclide-induced bone cancer and leukaemia, as compared to adults (Richardson 2009a). The ICRP provides Ca-like and Pu-like skeletal model parameters for adults (shown in Tables 1 and 2), as well as tabulating equivalent values for non-adults (ICRP 1993, ICRP 1995b). Skeletal growth and the consequent increase in bone turnover are accounted for in these ICRP skeletal models. For example, for the Ca-like elemental models the transfer rate (d^{-1}) from the non-exchangeable cortical volume to plasma is 100-fold greater for the 3 month old compared to an adult (ICRP 1995b).

Cell proliferation is an important factor for cancer risk in general (Streffer 2009). Nie and Richardson (2009a) hypothesized that the evaluation of the radiation dose to mesenchymal-stem cells that lie in close proximity to forming bone surfaces is a measure of a radionuclide's ability to induce bone cancer associated with bone growth or remodelling. Only ~4% of the total bone surface of adults is forming, whereas the forming bone surface of infants may occupy up to half of the surface area of trabecular bone, which is the most prevalent bone type in infants (ICRP 1995a). Therefore the forming bone surfaces of trabecular bone, but also those of the epiphyseal growth plates and the periosteum, are particularly relevant bone cancer 'targets' in non-adults and warrant representative biokinetic compartments (Richardson, In press).

Other studies provide supporting evidence for radiation bone cancer targets being primarily associated with remodeling or growing bone surfaces. First, infants have a higher risk of excess bone cancer than adults after being treated for ankylosing spondylitis with high doses of the short-lived alpha-emitter ^{224}Ra. Nekolla et al. (2000) estimated the excess relative risk (ERR) per unit bone surface equivalent dose to be 0.45, 0.17 and 0.04 ERR Sv^{-1} for acute low exposures to individuals 5, 30 and 60 years of age, respectively. Second, radium or external beam radiotherapy have the same spectrum of bone tumour types as adults with pre-existing bone lesions; therefore, radiogenic bone tumours may be associated with hypermetabolic Paget's disease of bone (Gössner 1999). Third, the great majority of post-irradiation osteosarcomas in both beagle dogs and humans are associated with high turnover trabecular bone or growth plates (Miller et al. 2003; Richardson, In press). Experimental studies in dogs also show that bone surface seeking radionuclides, e.g. ^{228}Th, ^{239}Pu, ^{241}Am, ^{249,252}Cf and short-lived ^{224}Ra, induce bone tumours associated with high marrow cellularity and bone turnover rates (Lloyd et al. 1997). Fourth, the endosteum associated with quiescent bone surfaces is hypoxic and radio-

resistant due to the 'oxygen effect', whereas stem/progenitor cells in the vicinity of forming bone are well vascularized and radiosensitive (Nie and Richardson 2009). Supporting evidence comes from the location of plutonium-induced osteosarcomas in humans (including Mayak workers) and beagle dogs showing a preference for well-vascularized trabecular bone sites in the central skeleton (Miller et al. 2003). The oxygen effect in marrow is also relevant to radiation-induced leukaemia. The hypoxic endosteum may be two- or three-times less sensitive as a leukaemia target, depending on whether the exposure is high- or low-LET radiation (Richardson 2008) compared to the haematopoietic stem/progenitor cells in the remaining (non-endosteal) red bone marrow within the trabecular cavities. A case has been made by Richardson (In press), based on a review of marrow stem cell research, that radiation dose assessments will be a better predictor of cancer risk by modifying the present ICRP marrow 'target' tissues. The recommendation is to partition the ICRP's current whole red bone marrow target for leukaemia and also to partition the bone cancer target into quiescent and forming bone stem cell niches. The change to the marrow targets was motivated by the poor match between the leukaemia and bone cancer incidences/mortalities compared with the risk evaluated from the radiation dose delivered to the present ICRP bone marrow targets of radium dial painters, Thorotrast patients and Mayak nuclear workers.

The PSM, unlike the ICRP skeletal models, has compartments specifically assigned to two forms of bones surfaces: quiescent and forming. The 'affinity ratio' – defined by Polig (1998) as the uptake on forming surfaces to quiescent surfaces – is an important parameter for biokinetic skeletal models. Polig chose a skeletal-wide affinity ratio of three for Pu and suggested a value of unity for Am. The skeletal model for Pu by Priest and Hunt (1979) has trabecular and cortical bone compartments that specifically allow for the burial of Pu by new bone, but no compartments for bone fluid or surfaces lining quiescent bone. Neither Leggett's (1992) or Polig's (1997) skeletal models have a compartment separate from quiescent bone surfaces that explicitly accounts for uptake by forming bone surfaces, subsequent mineralisation and burial within new bone. The skeletal model developed by O'Flaherty (1993) has both i) 'metabolically active' trabecular and cortical bone surfaces that incorporate Pb by growth, and ii) 'quiescent' bone surfaces in cortical bone only. O'Flaherty modeled the diffusion of Pb by radial progression from the Haversian canal via the canaliculi bone fluid permeating the osteons of cortical bone. However, canaliculi diffusion was not included in O'Flaherty's representation of trabecular bone. In contrast, the PSM has bone fluid compartments not only for cortical bone but also for trabecular bone; as the latter also has osteocytes and an accompanying lacuno-canaliculi network that drains to the bone marrow sinusoids (Burger and Klein-Nulend 1999).

Biokinetic simulations employing the PSM will, utilizing O'Flaherty's model, also result in remodeling processes dominating transport in trabecular bone, whereas the bone fluid pathway is more important in cortical bone. The PSM, uniquely for a skeletal model, proposes and incorporates a terminal or tertiary phase of mineralization that relies upon transportation of minerals by diffusion and mechanical-loading induced convection processes in bone fluid. This tertiary mineralisation takes place over a long period (limited only by lengthy bone turnover times) compared with the relatively rapid primary and secondary phases of mineralization. As the turnover of an adult's cortical bone volume is decades long, this results in a terminal value rising from 0.52 to 0.58 for the fraction of bone mass consisting of minerals, which is higher than the equivalent mineral content of trabecular bone (0.49 to 0.50) whose bone volume turnover is six-fold faster than cortical bone. There is some experimental evidence (but in general a paucity of quantitative parameter data) supporting a tertiary phase of mineralization. Subjects who are

pregnant, undergoing irradiation, experiencing microgravity, elderly or physically inactive can suffer from considerable bone loss (Hillsley and Frangos 1994; Richardson 2009b). In some circumstances the osteocytes may regulate a decline in mineralization, in addition to any change in bone remodeling rates. It can be surmised that lower physical activity/forces will lead to a drop in the load-induced bone fluid flow in the elderly, the bedridden and astronauts, which will consequently result in diminution of the tertiary phase of mineralisation. A lower bone fluid flow reduces the supply of nutrients (i.e., oxygen, glucose) and bone constituents (i.e., minerals, albumin) to the bone volume that may cause a detrimental decrease in bone density and an increase in osteocyte cell death, more unrepaired bone microcracks and a greater incidence of osteoporosis and pathological bone fractures (Schaffler et al. 1995).

In conclusion, the PSM has the following important characteristics. It allows separate biokinetics for organic and inorganic species in blood and the skeleton, especially during the bone remodelling process. It uniquely incorporates a tertiary phase of mineralization via bone fluids. The PSM's mass transfers, organ and tissue masses, and bone formation half times are based on anatomical and physiological criteria. Another feature of this model is the division of bone surfaces into biokinetically separate quiescent and forming bone entities, the latter representing osteoid producing new bone. The PSM is particularly suited to evaluate the biokinetics of radionuclides and stable elements in children, infants, and perhaps the third trimester fetus. Work is planned that involves evaluating the influence of whole body and skeletal growth on dose coefficients for the carbon radionuclide, ^{14}C in humans employing the physiological HCNO model for hydrogen, carbon, nitrogen and oxygen (Richardson et al. 2003). While parameter values for the PSM are given for the adult only in this paper, future work will employ the model for assessing the dosimetry of radionuclides in non-adults.

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FIGURES

Fig. 1. The ICRP skeletal model is shown for bone volume-seeking i.e., alkaline earth or Ca-like elements, Ca, Sr, Ba and Ra, plus Pb and U (ICRP 1993, ICRP 1995b), with the range of adult pathway half-times. A separate compartment for red blood cells that interacts only with the plasma compartment is not shown.

Fig. 2. The ICRP skeletal model is shown for bone surgace seeking, i.e. for actinides or Pu like elements, Th, Np, Pu, Am and Cm (ICRP 1993, ICRP 1995b) with the range of adult pathway half times.

Fig. 3 PSM compartments and adult pathway half times (filled arrowheads for dual organic and inorganic components and non-filled arrow heads for a single component only). The processes are shown by which material is transported. C, convection, D, diffusion, F, bone formation, and R, resorption. A separate compartment for red blood cells that interacts only with the plasma compartment shown.

Table 1.
ICRP adult bone model half-times (h, d or y) and rate constants, (d^{-1}), for Ca-like, bone volume-seeking elements (ICRP 1993, ICRP 1995b). The common ionic form in blood is given in brackets. Only the third column has data if the values are the same for all elements.

Pathways	Unit	Ca (Ca^{2+})	Sr (Sr^{2+})	Ba (Ba^{2+})	Ra (Ra^{2+})	Pb (Pb^{2+})	U (UO_2^{2+})
Plasma to trabecular bone surface	h	8.0	8.0	1.7	1.7	3.4	8.2
	d^{-1}	2.1	2.1	9.7	9.7	4.9	2.0
Plasma to cortical bone surface	h	10	10	2.1	2.1	4.3	10
	d^{-1}	1.7	1.7	7.8	7.8	3.9	1.7
Bone surfaces to plasma	d	1.2	1.2	1.2	1.2	1.4	10
	d^{-1}	0.58	0.58	0.58	0.58	0.50	0.069
Bone surfaces to exch bone volumes	d	6.0	6.0	6.0	6.0	1.4	10
	d^{-1}	0.12	0.12	0.12	0.12	0.50	0.069
Exch bone volumes to bone surfaces	d	250	161	72	38	38	40
	d^{-1}	0.0028	0.0043	0.0097	0.019	0.019	0.017
Exch bone volumes to nonexch volumes	d	167	161	165	151	151	120
	d^{-1}	0.0042	0.0043	0.0042	0.0046	0.0046	0.0058
Nonexch trabecular volume to plasma	y	3.9					
	d^{-1}	0.00049					
Nonexch cortical volume to plasma	y	23					
	d^{-1}	8.2×10^{-5}					

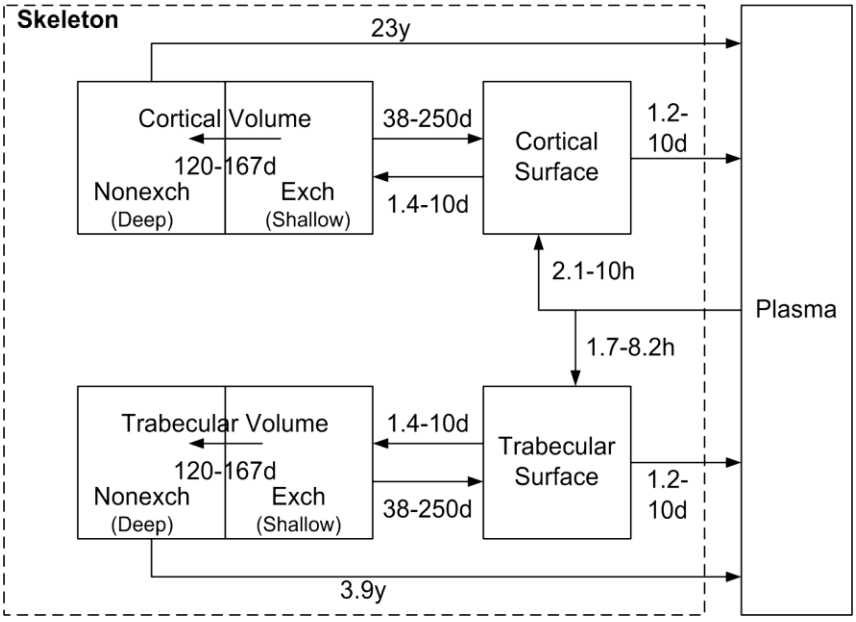
Table 2.
ICRP adult bone model half-times (h, d or y) and rate constants (d^{-1}) for Pu-like, bone surface-seeking elements (ICRP 1993, ICRP 1995b). The common ionic form in blood is given in brackets. Only the third column has data if the values are the same for all elements.

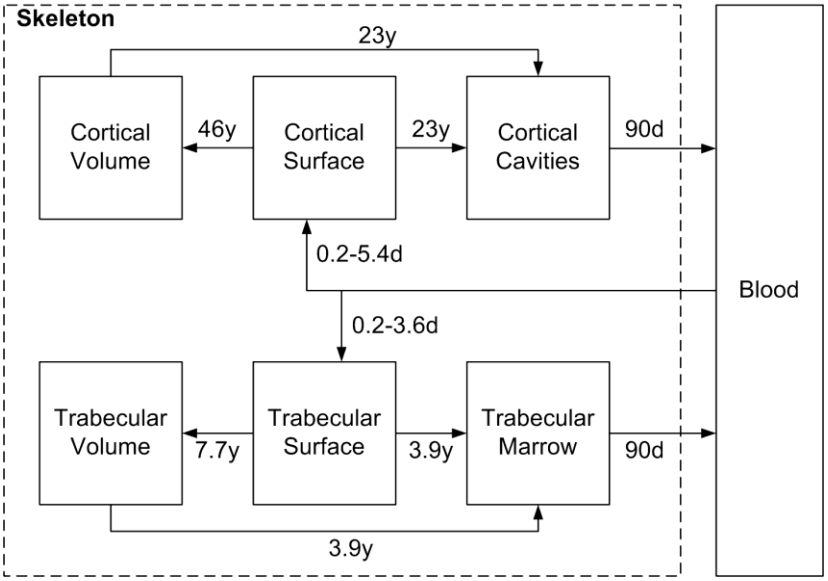
Pathways	Unit	Th (Th^{4+})	Np ($Np^{4+/5+}$)	Pu (Pu^{4+})	Am (Am^{3+})	Cm (Cm^{3+})
Blood to trabecular bone surface	h & d	1.0 d	1.4 d	3.6 d	4.8 h	4.8 h
	d^{-1}	0.68	0.48	0.19	3.5	3.5
Blood to cortical bone surface	h & d	1.0 d	1.8 d	5.4 d	4.8 h	4.8 h
	d^{-1}	0.68	0.39	0.13	3.5	3.5
Trabecular surface to volume	y	7.7				
	d^{-1}	0.00025				
Trabecular surface to marrow	y	3.9				
	d^{-1}	0.00049				
Cortical surface to volume	y	46				
	d^{-1}	4.1×10^{-5}				
Cortical surface to marrow	y	23				
	d^{-1}	8.2×10^{-5}				
Trabecular volume to marrow	y	3.9				
	d^{-1}	0.00049				
Cortical volume to marrow	y	23				
	d^{-1}	8.2×10^{-5}				
Cort./trab. bone marrow to blood	d	90				
	d^{-1}	0.0076				

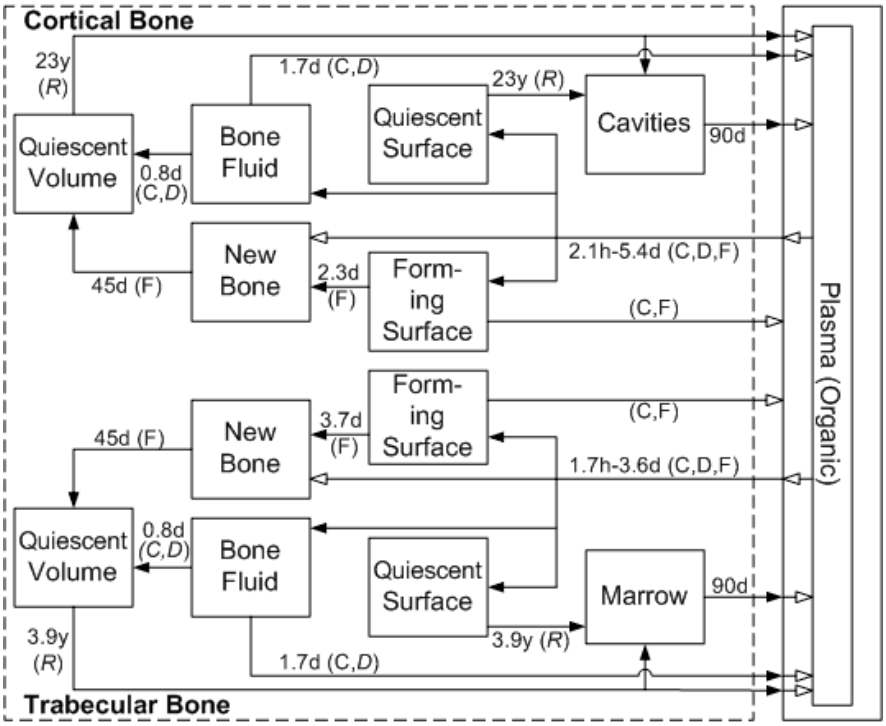
Table 3.
PBM parameters for the adult associated with compartmental composition and mass.

Compartments	Total bone surface (%)	Critical parameter	Mineral mass fraction	Density (g cm^{-3})	Mass (g)
Trabecular bone, total	*100* [a]	10.5 m^2			*1100*
Quiescent Surface	94.0	1 μm thick	0.50	1.90	19
Forming Surface	5	3 μm thick	0.18	1.39	2.2
New Bone	5	29 μm thick [b]	0.44	1.81	32
Quiescent Volume		Turnover 3.9y	0.50	1.90	1025
Bone Fluid		2% wet bone mass		1.00	22 (0.0022 gCa)
Cortical bone, total	*100* [a]	6.5 m^2			*4400*
Quiescent Surface	97.6	1 μm	0.58	2.07	13
Forming Surface	2	5 μm thick	0.21	1.45	0.9
New Bone	2	55-100 μm radius [c]	0.48	1.91	20
Quiescent Volume		Turnover 23y	0.58	2.07	4278
Bone Fluid		2% wet bone mass		1.02	88 (0.0088 gCa)

[a]: total bone surfaces: forming surfaces are 6 and 3% for cortical and trabecular bone, respectively according to ICRP (1995a): resorbing surfaces are one-fifth of forming. Values in table are modified based on measurements of Jowsey et al. (1965).
[b]: the average (slab) semi-osteon, 56 μm deep, is two-thirds filled with Forming Surface and New Bone.
[c]: the average (center-hole cylinder) osteon, 20 μm inner and 100 μm outer radius, is two-thirds filled with Forming Surface and New Bone.




Skeleton
23y
Cortical Volume
46y
Cortical Surface
23y
Cortical Cavities
90d
Blood
0.2-5.4d
0.2-3.6d
Trabecular Volume
7.7y
Trabecular Surface
3.9y
Trabecular Marrow
90d
3.9y


Cortical Bone
23y (R)
1.7d (C,D)
23y (R)
Quiescent Volume
0.8d (C,D)
Bone Fluid
Quiescent Surface
Cavities
90d
Plasma (Organic)
2.1h-5.4d (C,D,F)
45d (F)
New Bone
2.3d (F)
Form-ing Surface
(C,F)
(C,F)
45d (F)
New Bone
3.7d (F)
Form-ing Surface
1.7h-3.6d (C,D,F)
Quiescent Volume
0.8d (C,D)
Bone Fluid
Quiescent Surface
Marrow
90d
3.9y (R)
3.9y (R)
1.7d (C,D)
Trabecular Bone