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UPDATED BIOKINETIC MODEL FOR SYSTEMIC AMERICIUM

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Abstract

The biokinetic model for systemic americium (Am) currently recommended by the International Commission on Radiological Protection (ICRP) for application to occupational intake of Am is based on information available through the early 1990s. Much additional information on Am biokinetics has been developed in the past 25 y, including measurements of retention and excretion of ^{241}Am in many workers with ^{241}Am burdens and post mortem measurements of ^{241}Am in tissues of some of those workers. The ICRP's current Am model is reasonably consistent with the updated information, with the main exception that the current model apparently overestimates 24-hour urinary Am as a fraction of skeletal or systemic Am at late times after intake. This paper provides an overview of current information on the systemic kinetics of Am in adult human subjects and laboratory animals and presents an updated biokinetic model for systemic Am that addresses the discrepancies between the current database and current ICRP systemic model for Am. This model is applied in Part 4 (to appear) of an ICRP series of reports on intake of radionuclides by workers called the OIR (Occupational Intake of Radionuclides) series.

Introduction

Americium (Am) is an artificial element produced primarily in reactors by bombardment of plutonium (Pu) with neutrons and by radioactive decay of Pu or Cu (curium) isotopes. Americium-241 ($T_{1/2}$ = 432.2 y) is the most common Am isotope and typically one of the most abundant radionuclides in nuclear waste. Americium-241 is used as a component of smoke detectors, neutron sources, and discharge arresters and has been proposed as a long-lived energy source for thermoelectric generators. Americium-243 ($T_{1/2}$ = 7370 y) is the longest-lived Am isotope and the second most important Am isotope from the standpoint of radiation protection because of its long-term presence in nuclear wastes.

The biokinetic model for systemic (absorbed) Am currently recommended by the International Commission on Radiological Protection (ICRP) is based on information available through the early 1990s. The original version of the model (Leggett 1992) depicts changes with age in Am biokinetics from birth through late adulthood. A modified version of the model with age-invariant parameter values for adults was adopted in ICRP Publication 67 (1993) for derivation of dose coefficients for intake of radionuclides by members of the public. The ICRP's Am model for adult members of the public was applied to occupational intake of Am in ICRP Publication 68 (1994) and Publication 78 (1997). In this paper the current ICRP model for systemic Am is referred to as the "Pub. 67" model for Am for historical reasons, although attention is restricted here to the biokinetics of Am in adults.

Additional information on Am biokinetics in the human body has been developed since the completion of the Pub. 67 model, including long-term measurements of retention and excretion of ^{241}Am and the distribution of ^{241}Am determined at autopsy in accidentally or routinely exposed workers. The ICRP's current Am model appears to be reasonably consistent with the updated information, with the main exception that two studies on workers exposed to ^{241}Am or its parent ^{241}Pu suggest that the current model may overestimate daily urinary Am as a fraction of skeletal or systemic Am at times beyond a few thousand days after exposure. This paper provides an overview of current information on the systemic kinetics of Am in adult human subjects and laboratory animals and presents a revised biokinetic model for systemic Am that addresses the discrepancies between the current database and current ICRP systemic model for Am. This revised model is applied in Part 4 of an updated ICRP series of reports on intake of radionuclides by workers, called the OIR (Occupational Intake of Radionuclides) series (ICRP 2019, to appear).

Overview of the database

Human studies

The biokinetics of systemic Am has been investigated in workers exposed to ^{241}Am or its parent ^{241}Pu, which is tenaciously retained in systemic tissues and decays to ^{241}Am with a half-time of 14.4 y. Reported biokinetic data for ^{241}Am in workers include urinary and faecal activity and external measurements of activity in bone and liver of living subjects, and ^{241}Am in a liver, bone, and other tissues collected at autopsy.

Data for direct intake of relatively pure ^{241}Am (i.e., not mixed with a significant amount of its parent ^{241}Pu) are preferred for modelling Am kinetics but are available only for a relatively

small number of subjects, some of whom received chelation therapy (Wrenn et al 1972; Whalen and Davies 1972; Fry 1976; Rosen et al 1980; Heid and Robinson 1985; Breitenstein and Palmer 1989; Doerfel and Oliveira 1989; Kathren et al. 2003; Malátová et al 2003, 2010). More extensive observations are available for workers whose systemic ^{241}Am burdens are thought to have resulted from ingrowth of ^{241}Am in the body following intake of ^{241}Pu, or from some combination of ingrowth from deposited ^{241}Pu and direct intake of small amounts of ^{241}Am (Kathren et al 1988, 1997; Lynch et al, 1989; Popplewell and Ham, 1989; McInroy et al 1989; Kathren and McInroy 1992; Suslova et al 2013). Data for Pu workers with little potential for direct intake of ^{241}Am suggest that ingrown ^{241}Am migrates from its parent ^{241}Pu over time, resulting in a urinary excretion rate and a skeleton to liver activity ratio (i.e., ratio of total activity in the skeleton to that in liver) that are much higher for ^{241}Am than for its parent. However, ^{241}Am produced in bone and perhaps at some soft-tissue sites may remain with ^{241}Pu for an extended period. Thus, ^{241}Am produced *in vivo* by decay of ^{241}Pu may reflect some combination of the biokinetic characteristics of Am and distinctive characteristics of Pu.

Sokolova et al (2013, 2014) assessed the potential contributions of direct intake and *in vivo* production of ^{241}Am to its total body content in workers at the Mayak Production Association. The analysis was based on autopsy data, biokinetic models for Pu and Am, and consideration of the relative concentrations of ^{241}Am and Pu isotopes in air over time at different work locations at Mayak. The investigators concluded that the contribution of direct intake of ^{241}Am to the body burden of ^{241}Am depended on dates of employment at Mayak. The ^{241}Am burdens in subjects who started and ended work at Mayak prior to the 1970s were likely to have arisen almost entirely from decay of internally deposited ^{241}Pu. At the other extreme, in workers who started and ended work after the 1990s, almost all the ^{241}Am burden was likely to have arisen from direct intake of ^{241}Am. Data shown graphically for ~200 workers who started work from the late 1940s through the 1980s indicate that in most cases, ^{241}Am taken directly into the body represented a greater portion of the body burden than ^{241}Am produced *in vivo*.

Americium-241 has been measured in the total body or selected tissues of many United States Transuranium and Uranium Registry (USTUR) donors with occupational exposures to ^{241}Pu or mixtures of ^{241}Pu and ^{241}Am and in a few cases to relatively pure forms of ^{241}Am. Most of the exposures are thought to have occurred two or more decades before death. The ratio of the ^{241}Am content of the skeleton to that of the liver was estimated by the authors of the present paper for 101 USTUR cases (Kathren et al 1988, 1996a, 1996b, 1997; McInroy et al 1989; Filipy and Kathren 1996; Filipy 2001, 2002, 2003) under the assumption that reported ^{241}Am concentrations for bone samples were representative of the entire skeleton. The estimated skeleton to liver ratio ranged from 1.2 to 89 with a mean of 15 and median of 7.8. For seven whole body donors (McInroy et al 1989, Filipy 2003) the ^{241}Am contents of the skeleton, liver, and other soft tissues represented on average 74.2%, 7.9%, and 17.9%, respectively, of systemic ^{241}Am. Median values were 77.7%, 6.5%, and 13.5%, respectively. Blanchardon et al (2007) reviewed USTUR data on the distribution of ^{241}Am in workers and attempted to determine a typical fractional content of ^{241}Am in soft tissues other than liver and kidneys. They concluded that the most reliable data, as judged mainly from the sampling process for massive tissues and the level of activity in the samples, indicated that soft tissues excluding liver and kidneys typically contain roughly 15% of systemic ^{241}Am.

A detailed autopsy study of the tissue distribution of ^{241}Am was conducted for a radiochemist (USTUR Case 102) thought to have been exposed through contamination of a wound while working with an unsealed ^{241}Am source during the period 1952-54, about 25 y before his

death at age 49 y (Breitenstein et al. 1985, Heid and Robinson 1985, McInroy et al. 1985, Durbin and Schmidt 1985). The first indication that an intake had occurred was detection of radioactivity in a urine sample collected in 1958 as part of a routine surveillance program. No chelation therapy was performed, although Ca-EDTA was used on one occasion to cause sufficient excretion of activity to identify the radionuclide. The skeleton, liver, kidneys, and other soft tissues contained 82.3%, 6.4%, 0.25%, and 11.0%, respectively, of the systemic burden. About 80% of skeletal activity was contained in compact bone together with the portion of trabecular bone containing fatty marrow, and the remaining 20% was in trabecular bone containing red marrow. Activity was distributed among bone groups as follows: skull (including mandible), 13.6%; vertebrae, 10.6%; arms and hands, 13.2%; legs and feet, 46.0%; ribs, 5.7%; pelvis, 7.2%; remaining bones, 3.7% (Lynch et al. 1989). The large portion of activity found in the lower extremities may be unusual as the subject's legs contained a considerably larger portion of skeletal mineral than measured in age-matched controls, presumably resulting from the subject's long-term strenuous program of running and bicycling (Durbin and Schmidt 1985, Lynch et al. 1989). Durbin and Schmidt (1985) noted evidence of a gradual trend toward uniform distribution of ^{241}Am in the skeleton and extrapolated the findings for this subject to the following distribution in an adult with a typical distribution of bone mineral: cranium and mandible, 17.9%; vertebrae, 12.2%; arms and hands, 15.2%; legs and feet, 38.2%; ribs, 6.3%; pelvis, 6.3%; remaining bones, 3.9%.

Malátová et al (2003, 2010) measured ^{241}Am in urine and faeces and externally in the skull in seven workers for periods up to about 11 y, starting about 11-25 y after their suspected times of highest exposure to relatively pure ^{241}Am. The main source of contamination presumably was AmO_2 powder, used in the production of AmBe neutron sources, smoke alarms, and other ^{241}Am sources. The estimated content of ^{241}Am in the skull was extrapolated to the total skeleton based on the assumption that the skull contains 12.5% of skeletal ^{241}Am (Lynch et al 1989). The investigators compared their findings with predictions of the model for systemic Am in adults adopted in ICRP Publications 67 (1993) and applied to workers in Publications 68 (1994) and 78 (1997). The data were judged to be consistent with the urinary to faecal excretion ratio predicted by that model but to indicate a lower than predicted ratio of daily urinary ^{241}Am to skeletal ^{241}Am. Estimation of inaccuracies in the model's representation of retention or excretion of systemic Am based on this data set is complicated by several factors including uncertainty in exposure times, irregular patterns of urinary ^{241}Am in individual subjects, and a changing composition of the study group when observations are plotted against the best estimate of time after exposure.

Suslova et al (2013) studied the distribution and excretion of ^{241}Am and Pu isotopes in workers at the Mayak Production Association. Presumably a substantial portion of ^{241}Am was produced *in vivo* by decay of internally deposited ^{241}Pu in most of the studied workers. Autopsy data were obtained for 290 workers who died on average 14.7 y ± 12 y (standard deviation) after the end of employment; their periods of employment ranged from 1 to 46 y. Urine bioassay measurements were performed about 23-26 y after the end of employment for 47 workers who started work at Mayak from 1949-1964, a period of high inhalation exposures. Twenty-seven of the subjects had worked in a Pu production facility, and 20 had worked in a radiochemical facility. The time from beginning of exposure to bioassay averaged about 44 ± 7 (SD) y for each group. Subjects of the autopsy study were divided into two groups by cause of death and histopathological findings in the liver. Group 1 consisted of 33 subjects who died from suicide, accident, or acute cardiovascular problems. Group 2 consisted of 257 subjects with various liver diseases or other chronic illnesses over an extended period before death. For Group 1 the skeleton, liver, kidneys, and other soft tissues contained on

average 69.3%, 23.1%, 0.44%, and 7.2%, respectively, of systemic ^{241}Am; and 46.4%, 46.0%, 0.17%, and 7.4%, respectively, of systemic Pu. For Group 2 the skeleton, liver, kidneys, and other soft tissue contained on average 80.6%, 11.1%, 0.17%, and 8.1%, respectively, of systemic ^{241}Am; and 65.3%, 25.8%, 0.16%, and 8.7%, respectively, of systemic Pu. The average ratio of daily urine excretion of ^{241}Am to total systemic ^{241}Am based on whole body counting of 29 reasonably healthy workers was about 1.8×10^{-5} (SD, 1.0×10^{-5}). The ratio of daily urine excretion of ^{241}Am to total systemic ^{241}Am based on autopsy measurements averaged about 1.6×10^{-5} (SD, 0.63×10^{-5}) for seven reasonably healthy workers and about 2.9×10^{-5} (SD, 2.4×10^{-5}) for 15 unhealthy workers.

Animal studies

The behaviour of Am in blood has been studied in a variety of animals including baboons (Rosen et al 1972, Cohen and Wrenn 1973, Guilmette et al 1980), monkeys (Durbin 1973), beagles (Bruenger et al 1969), sheep (McClellan et al 1962), rats (Turner and Taylor 1968, Belyaev 1969, Priest 2007), cows (Sutton et al 1978), and goats (Sutton et al 1978). Nearly all Am in blood is found in the plasma fraction. As is the case for Pu and neptunium (Np), most circulating Am is bound to plasma proteins, primarily transferrin and citrate. However, the affinity constants are much lower for Am than for Pu or Np, resulting in much faster removal of Am from blood (Paquet and Stather 1997). Roughly 5-10% of intravenously injected Am remains in blood at 1 h, 0.1 1.5% at 24 h, and 0.03-0.5% at 48 h. Much of the activity that leaves blood in the first hour after injection returns to blood over the next few hours.

Data for rats suggest that a third or more of Am leaving blood in the first few minutes after injection entered soft tissues and extracellular fluids and that much of this returned to blood over the next few hours (Belyaev 1969, Durbin 1973). In baboons, a substantial portion of systemic Am remained in the non-liver soft tissues at 1 d (Guilmette et al 1980).

Following parenteral administration of ^{241}Am citrate to baboons (Rosen et al 1972, Cohen and Wrenn 1973), monkeys (Durbin 1973), and beagles (Lloyd et al 1970), cumulative urinary excretion over the first 3 weeks amounted to ~10% of the administered activity. In beagles the urinary excretion rates over the first three weeks were similar for Am and Cm (curium) isotopes (Lloyd et al 1970, Lloyd et al 1974). Similar urinary excretion rates were observed for Am and Cm in rats following parenteral administration (Durbin 1973).

In animals of all ages, most systemic Am (typically 80% or more) accumulates in the skeleton and liver within a few days after parenteral injection (Lloyd et al 1970, Rosen et al 1972, Durakovic et al 1973, Stevens et al 1977, Guilmette et al 1980). In monkeys (Durbin 1973) and beagles (Lloyd et al 1970) the liver and skeleton contained about 50% and 30%, respectively, of the systemic activity in the first few days or weeks after injection. In baboons (Guilmette et al, 1980) the liver and skeleton contained about 30% and 40%, respectively, of systemic activity in the early weeks after injection.

The kinetics of Am in the liver varies among species. The studied animal species fall into two main groups (Taylor 1984, Durbin and Schmidt 1985). A group including rats, mice, macaque monkeys, and baboons shows a short residence time in the liver and a relatively high rate of removal of activity in bile. A second group including dogs and hamsters shows much slower removal from the liver with relatively low loss via biliary secretion. Biological half-times of Am in the liver typically are on the order of 5-15 d in rats and mice, 30-150 d in baboons and monkeys, and a few years in dogs and hamsters. Long-term studies on dogs (Lloyd et al 1970,

Mewhinney et al 1982) indicate that a large portion of the initial liver burden gradually transfers to the skeleton.

Hamilton (1948) described the sites of bone deposition of Am and Cm in rodents as indistinguishable from those of the trivalent elements cerium, promethium, and actinium but different from sites of deposition of the tetravalent elements plutonium, thorium, and zirconium. Later studies involving a variety of animal species indicate that Am deposits on all types of bone surfaces, including resorbing and forming surfaces (Herring 1962, Lloyd et al 1972, Durbin 1973, Priest et al, 1983). Deposition on bone surfaces is considerably more uniform than that of Pu, which deposits largely on endosteal bone surfaces. In dogs and monkeys, initial concentrations of Am on bone surfaces tended to decrease in the order: resorbing surfaces > resting surfaces > growing surfaces (Herring 1962, Lloyd et al 1972, Durbin 1973). Am deposits to a much greater extent than Pu on Haversian surfaces of cortical bone (Hamilton 1948, Herring et al 1962).

Priest et al (1983) studied the systemic behaviour of ^{241}Am in rats over the first month after administration, with emphasis on its behaviour in bone. After 1 d the total body contained about 90% of the injected activity. At that time the liver and skeleton contained roughly one-half and one-third, respectively, of the injected amount. The liver content declined with a half-time of about 12 d. Most of the loss from the liver presumably entered the gastrointestinal content in bile, but a gradual increase in the skeletal content over the observation period indicated that part of the activity removed from the liver re-entered the circulation. Activity entering the skeleton deposited on all types of bone surfaces including vascular canals within cortical bone but was preferentially deposited on resorbing surfaces. Bone accretion resulted in burial of surface deposits. Bone resorption caused removal of ^{241}Am from surfaces and its accumulation in phagocytic cells in bone marrow. Some "local recycling" of ^{241}Am back to bone surfaces appeared to occur. That is, it appeared that some activity was redeposited on bone surfaces near sites of bone resorption, rather than transferring to the general circulation. Some "systemic recycling" of resorbed activity (i.e., transfer to the general circulation and subsequent redeposition on bone surface) may also have occurred. Within the skeleton the largest increases in the ^{241}Am content over the observation period were found for bones with relatively low resorption rates.

Comparison of the long-term gross distributions of skeletal Am and Pu in dogs indicated more similarities than differences (Lloyd et al 1972). A notable difference was that the skeletal distribution of Pu changed little with time after injection while the distribution of Am changed noticeably over time. In particular, three bones with high trabecular content (vertebrae, tail, and sternum) exhibited a decreasing fraction of total skeletal Am with increasing time.

Updated model for systemic Am

Description of the model

This section describes a modified version of the model for systemic Am in adults adopted in ICRP Publication 67 (1993) and applied to workers in Publications 68 (1994) and 78 (1997). The modifications are made for two reasons: (1) to achieve closer agreement with updated information indicating that the model of Publication 67 overestimates the rate of excretion of systemic ^{241}Am at times remote from uptake to blood; and (2) for consistency with the generic structure of the model for liver used in Part 4 of the ICRP's series of reports on occupational intake of radionuclides (ICRP 2019, to appear).

The following changes are made to the Am model used in Publication 67:

- In the generic structure for the liver applied to actinide elements in OIR Part 4, the liver is divided into compartments with relatively fast and relatively slow turnover. For Am the biological half-time assigned to the fast-turnover compartment (Liver 1) is the default value (30 d) for actinides and lanthanides. A removal half-time of 1 y, the half-time applied to the single liver compartment in the Pub. 67 model, is applied in the revised model to the liver compartment with relatively slow turnover (Liver 2).
- The removal half-time from gonads is reduced from 10 y to 5 y, a generic value applied in the OIR reports to the actinides and lanthanides based mainly on analogy with the frequently studied elements Pu and Ce (cerium) (Thomas et al., 1989; Taylor and Leggett 2003; Leggett et al. 2014).
- The generic bone model is modified for application to Am in view of data indicating that the model of Publication 67 probably overestimates the ratio of daily urinary ^{241}Am to skeletal ^{241}Am at times remote from intake. A simple resolution of this discrepancy between model predictions and observations that has some experimental basis is to depict explicitly local recycling of a sizable portion of Am resorbed from cortical bone. That is, activity removed from bone surface by bone remodelling may be redeposited at adjacent sites of bone formation without returning to the general circulation (ICRP 1995). Such local recycling of skeletal ^{241}Am appeared to occur in rats (Priest et al 1983). In a review of the physiology of bone mineral, Parfitt and Kleerekoper (1980) concluded that some mineral removed by osteoclasts during remodelling of cortical bone will be redeposited almost immediately at closely adjacent sites of bone formation supplied by the same blood vessels. They suggested that local recycling might also occur to some extent in trabecular bone but that there is a greater possibility that material resorbed from trabecular bone, which is generally much more vascularized than cortical bone, will escape to the general circulation. In the revised model, local recycling is assumed to occur only in cortical bone. Implementation of local recycling requires a modification of the generic bone model for bone-surface seekers. In the generic model, activity removed from bone is assumed to transfer to bone marrow and subsequently from bone marrow to blood. The generic bone model is modified here for application to Am by assuming that a fraction F of the amount entering cortical marrow subsequently transfers to cortical surface (local recycling), and the fraction 1-F transfers to blood. The removal half-time from cortical marrow to all destinations remains at the generic value of 0.25 y. A local recycling fraction F=2/3 is selected for reasonable consistency with reported data on the long-term relation of ^{241}Am in bone and urinary ^{241}Am, taking account of limitations in the reported data. The removal half-time from cortical bone marrow to all destinations remains at the generic value of 0.25 y.

The structure of the modified model for Am is shown in Figure 1. Transfer coefficients for Am in adults are listed in Table 1.

Transfer coefficients are based on the following deposition fractions and half-times, most of which are carried over from the Am model for adults adopted in ICRP Publication 67. Americium leaves blood with a half-time of 30 min, with 30% (deposition fraction 0.3) going to a soft-tissue compartment called ST0 that exchanges activity relatively quickly with blood and is considered part of the circulation. The following deposition fractions for other pools

refer to activity that leaves the circulation: liver, 0.5; cortical bone surface, 0.15; trabecular bone surface, 0.15; right colon content, 0.013; urinary bladder content, 0.07; urinary path (a compartment of the kidneys that feeds the urinary bladder content), 0.02; other kidney tissue, 0.005; testes, 0.00035; ovaries, 0.00011; ST2 (soft-tissue compartment with slow turnover), 0.02; and ST1 (soft-tissue compartment with an intermediate turnover rate, the remaining ~0.072. The ICRP's generic bone model for bone-surface-seeking radionuclides (ICRP 2015) is applied to activity depositing on bone surface, with the exception that a portion of activity deposited in cortical bone marrow is assumed to be locally recycled, i.e., to transfer to cortical bone surface, as described in the preceding paragraph. Specifically, activity is removed from cortical bone marrow with a biological half-time of 0.25 y, with 2/3 of the outflow depositing on cortical bone surface and 1/3 transferring to blood. The following biological half-times are applied to non-skeletal tissue compartments: liver to blood and small intestine content, 1 y, with 97.4% returning to blood and 2.6% going to small intestine content in bile; gonads to blood, 10 y; urinary path to urinary bladder content, 7 d; other kidney tissue to blood, 500 d; ST0 to blood, 0.5 d; ST1 to blood, 50 d; and ST2 to blood, 100 y.

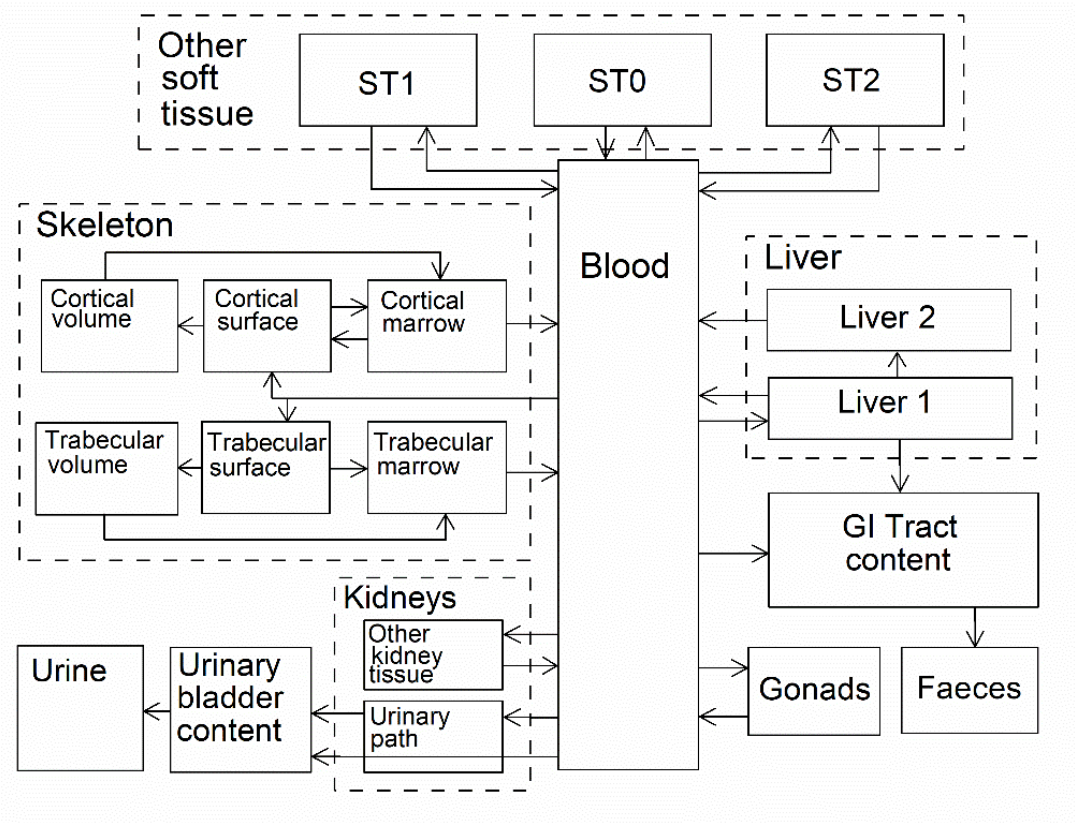

Figure 1. Structure of the updated systemic model for americium.

Comparison of predictions of Pub. 67 model and updated model

Predictions of retention and excretion of ^{241}Am following acute input into blood of an adult based on the updated Am model described in this paper are compared in Figure 2 with predictions of Pub. 67 model. Little difference in predictions of the two models is seen over the first few years after injection. Subsequently, total-body retention based on the updated model becomes noticeably greater than retention based on the Pub. 67 model. This results mainly from the updated model's prediction of greater retention in the skeleton (specifically, in cortical bone) and consequently a lower excretion rate at late times than predicted by the Pub. 67 model. Differences in predictions of the time-dependent liver content are modest in absolute terms, although the Pub. 67 model predicts roughly a twofold higher liver content than does the updated model at late times due to lower predicted feedback from cortical bone to blood. For example, at 25 y after injection of ^{241}Am into blood, the Pub. 67 model predicts that liver, skeleton, kidneys, and remaining tissues contain, respectively, 7.4%, 78.8%, 0.11%, and 13.6% of total-body activity. The updated model predicts corresponding values of 4.4%, 84.6%, 0.06%, and 11%, respectively. Both sets of values are reasonably consistent with the distribution found in the detailed autopsy study described earlier of a chemist with a relatively high intake of ^{241}Am via a wound about 25 y before death. The two models predict roughly the same ratio of cumulative urinary Am to cumulative faecal Am.

Table 1. Transfer coefficients in the biokinetic model for systemic Am		
From	To	Transfer coefficient (d^{-1})
Blood	Liver 1	11.6
Blood	ST0	10.0
Blood	ST1	1.67
Blood	ST2	0.466
Blood	Cortical bone surface	3.49
Blood	Trabecular bone surface	3.49
Blood	Kidneys 1	0.466
Blood	Right colon content	0.303
Blood	Kidneys 2	0.116
Blood	Testes	0.0082
Blood	Ovaries	0.0026
Blood	Urinary bladder content	1.63
Liver 1	Small intestine content	0.0006
Liver 1	Liver 2	0.0225
Liver 2	Blood	0.0019
ST0	Blood	1.386
ST1	Blood	0.0139
ST2	Blood	0.000019
Cortical bone marrow	Blood	0.00253
Cortical bone marrow	Cortical bone surface	0.00507
Cortical bone surface	Cortical bone marrow	0.0000821
Cortical bone surface	Cortical bone volume	0.0000411
Cortical bone volume	Cortical bone marrow	0.0000821
Red marrow	Blood	0.0076
Trabecular bone surface	Red marrow	0.000493
Trabecular bone surface	Trabecular bone volume	0.000247
Trabecular bone volume	Red marrow	0.000493
Kidneys 1	Urinary bladder content	0.099
Kidneys 2	Blood	0.00139
Testes	Blood	0.00038
Ovaries	Blood	0.00038

Table 2 compares 50-y predicted integrated activities (number of nuclear transformations, or nnts) in various systemic tissues and fluids based on the updated model and Pub. 67 model, assuming injection of ^{241}Am to blood at time zero. The comparisons are expressed as ratios A:B, where A and B are the integrated activities based on the updated model and Pub. 67 model, respectively. The ratios are greater than 1.0 for cortical bone surface, volume, and marrow, and for the total body, and are less than 1.0 for all other regions. For tissues other than gonads, this pattern of ratios is due to the assumption in the updated model of local recycling of activity released from cortical bone. This results in greater accumulation of ^{241}Am in cortical regions over time, leaving smaller amounts available for deposition in other tissues and in the urinary bladder content. The relatively low ratios A:B for gonads results partly from the lower feedback from cortical bone to blood but mainly from the shorter biological half-time assumed for gonads in the updated model.

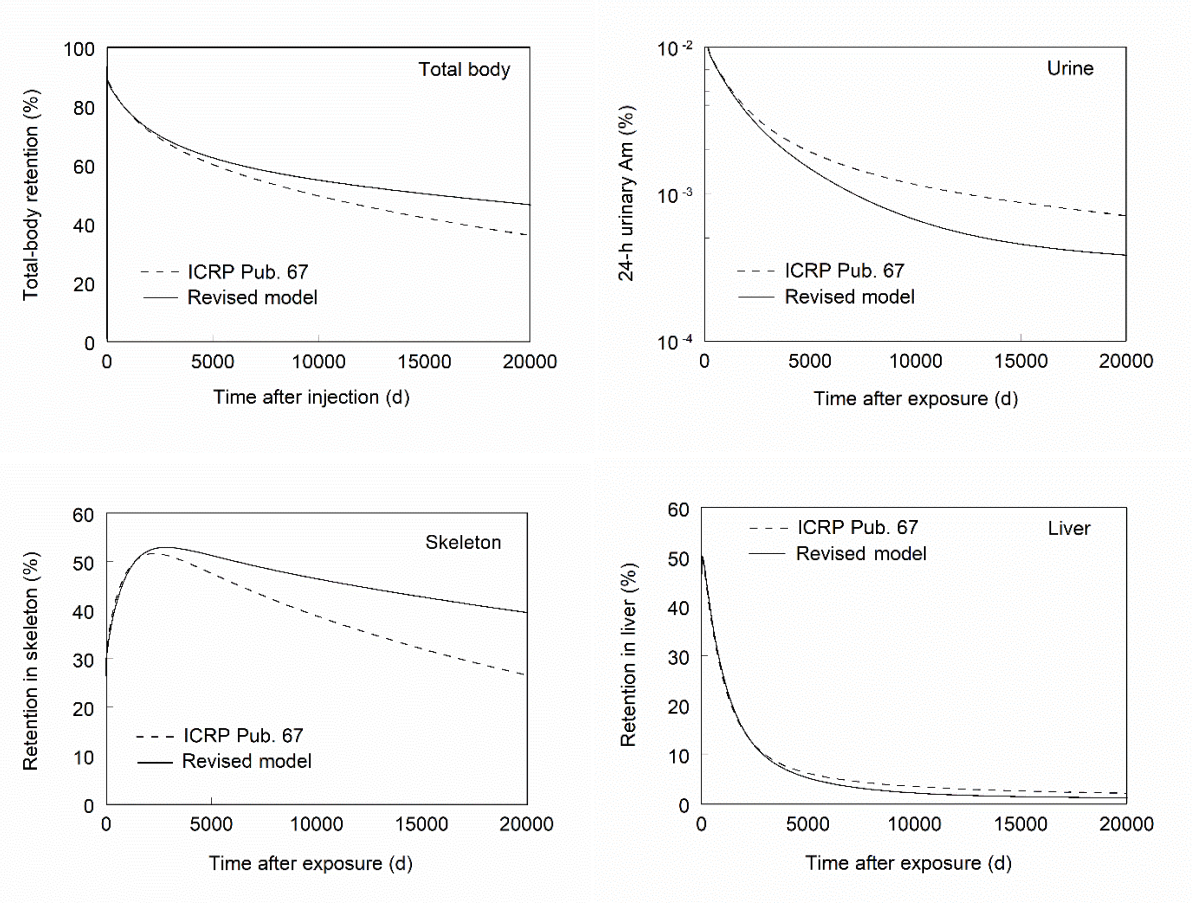

Figure 2. Comparison of predictions of the ICRP Publication 67 (1993) model for Am with the revised model described here, assuming injection of ^{241}Am into blood of an adult at time zero.

Table 3 compares dose coefficients based on the Pub. 67 and updated models for systemic Am, for the case of injection of ^{241}Am into blood of an adult. The comparisons are expressed as ratios A:B, where A and B are dose coefficients based on the updated model and Pub. 67 model, respectively. Each of the systemic models was connected to the ICRP's Human Alimentary Tract Model (2006) to model the behaviour of activity secreted into the alimentary tract. The dosimetry system of ICRP Publication 135 (2016) and tissue weighting factors of ICRP Publication 103 (2007) were applied in each case. The same ratios of tissue doses were derived for adult males and females.

Table 2. Comparison of predicted numbers of nuclear transformations (nnts) in model regions over 50 y after injection into blood based on the Pub. 67 and the updated model for systemic Am presented here.	
Region	Ratio of nnts over 50 y Updated model : Pub. 67 model
Blood	0.82
Urinary bladder content	0.82
Liver	0.87
Kidneys	0.83
Gonads	0.46
Cortical bone surface	1.26
Cortical bone volume	1.19
Cortical marrow	1.25
Trabecular bone surface	0.83
Trabecular bone volume	0.84
Trabecular marrow	0.84
Other tissue	0.88
Total body	1.09

Table 3. Comparison of dose coefficients (Sv/Bq) for injection of ^{241}Am into blood of an adult, based on Pub. 67 model and the updated model for systemic Am presented here.	
Tissue	Ratio of dose coefficients[a] Updated model : Pub. 67 model
Endosteal bone surface	1.00
Kidneys	0.83
Liver	0.87
Red marrow	0.83
Gonads	0.46
Other tissues[b]	0.88[b]
Effective dose	0.81

[a]The ratios of the derived tissue dose coefficients are the same for males and females when rounded to two significant digits.
[b]The value 0.88 was derived for Brain, Breast, Colon, Lungs, Oesophagus, Salivary glands, Skin, Stomach wall, Thyroid, Urinary bladder wall

Discussion

The ICRP's current biokinetic model for systemic Am was developed in the early 1990s (Leggett, 1992) and adopted by the ICRP in Publication 67 (1993), which addressed doses to members of the public from ingestion of radionuclides. The Pub. 67 model with parameter values developed for adult members of the public was used in ICRP Publication 68 (1994) for derivation of dose coefficients for occupational intake of Am isotopes and in ICRP Publication 78 (1997) for derivation of reference bioassay data for application to intake of ^{241}Am by workers.

Much additional information on Am biokinetics has been developed since the early 1990s, including measurements of retention and excretion of ^{241}Am in many workers with ^{241}Am burdens and post mortem measurements of ^{241}Am in tissues of some of those workers. The updated information for workers may be divided into two categories: data for intake of relatively pure ^{241}Am; and a much larger set of data for workers exposed mainly to Pu isotopes including ^{241}Pu but sometimes mixed with ^{241}Am in quantities that exceeded subsequent production of ^{241}Am from *in vivo* decay of ^{241}Pu (Sokolova et al 2013, 2014). Comparisons of the two data sets and consideration of some known differences in the systemic behaviour of Pu and Am in the human body indicate that ^{241}Am produced *in vivo* by decay of ^{241}Pu probably migrates to a large extent from ^{241}Pu over time and behaves as if entering blood as a parent radionuclide. Removal of ^{241}Am from a site of decay of ^{241}Pu in bone may result only from the relatively slow process of bone restructuring, although it is conceivable that ^{241}Am born on bone surface could be removed by faster processes.

For the most part, the Pub. 67 model for systemic Am appears reasonably consistent with the updated biokinetic data for ^{241}Am in human subjects, but results of two studies on workers indicate that the Pub. 67 model may overestimate the Am excretion rate at times remote from intake. One of the studies involved workers exposed decades earlier to ^{241}Pu perhaps mixed in many cases with nontrivial ^{241}Am activity (Suslova et al. 2013). The other study involved intake of relatively pure ^{241}Am by workers (Malátová et al 2003, 2010).

In the study by Suslova et al (2013) summarized earlier, the distribution and excretion of ^{241}Am were measured in former Pu workers at Mayak. Based on typical levels of exposure to Pu over time at Mayak and the summary of bioassay times relative to employment years for the subjects of the study, it seems likely that the preponderance of exposures occurred at least 2-3 decades and perhaps up to 5 decades before bioassay times. The mean ratio R of 24-h urinary excretion of ^{241}Am to total systemic ^{241}Am was about 1.7×10^{-5}, depending slightly on the group of workers considered: $(1.8 \pm 1.0) \times 10^{-5}$ (mean ± standard deviation) for 27 healthy subjects with ^{241}Am systemic burdens based on externally measured ^{241}Am, and $(1.6 \pm 0.63) \times 10^{-5}$ for 7 healthy workers (i.e., considered reasonably healthy up to the time of sudden death) with ^{241}Am systemic burdens based on autopsy data.

We compared the "observed" mean ratio $R \approx 1.7 \times 10^{-5}$ determined by Suslova et al. (2013) for Pu workers with model projections based on either the systemic Am model of Pub. 67 or the updated systemic model for Am described in this paper. Calculations were performed for acute injection into blood of pure ^{241}Pu, pure ^{241}Am, or mixtures of ^{241}Pu and ^{241}Am. Model predictions of the ratio of urinary ^{241}Am to systemic ^{241}Am were compared with R for times in the range 25-50 y post injection. The Pu model of Leggett et al. (2005) was used to predict the time-dependent distribution of decays of ^{241}Pu in the body. Americium-241 produced in a systemic compartment by decay of ^{241}Pu was assumed to follow the kinetics described by the

applied Am model. This implies, for example, that ^{241}Am produced *in vivo* remained with ^{241}Pu in bone until removed by bone remodelling but was removed from liver much faster than ^{241}Pu. Predicted ratios of 24-h urinary excretion of ^{241}Am to total sys temic ^{241}Am based on the Pub. 67 Am model were in the range (2.2-3.4) x 10^{-5} for any given time between 25 and 50 y post injection and for any combination of ^{241}Pu and ^{241}Am entering blood at time zero, and hence were always greater than the observed mean ratio of 1.7 x 10^{-5}. Ratios based on the updated Am model were in the range (0.84-2.5) x 10^{-5} and hence bounded the observed mean ratio. For either of these models for systemic Am, the projected ratio of urinary Am to systemic Am decreased monotonically with increasing time after injection and with increasing percentages of ^{241}Am in the injected activity.

In the study by Malátová et al (2003, 2010), ^{241}Am was measured in excreta and externally in the skull in 7 workers exposed to relatively pure ^{241}Am. As stated by Malátová et al (2010, page 496): "The time of exposure was estimated mainly using records of the whole-body counting laboratory from the 1970s and interviews with individual workers. Worker JH was removed from all work with unsealed sources to administration after massive internal contamination had been found. As no such exact information existed about the other workers, the time of exposure was usually set in the middle of the monitoring interval." The derived time-dependent ratios U:S for individual subjects, where U = daily urinary ^{241}Am and S = total skeletal ^{241}Am, generally were much lower than predicted by the Pub 67 model, particularly at times greater than about 8500 d after the suspected times of highest exposure. As discussed below, the ratios U:S determined by Malátová and coworkers involve considerable uncertainties and some sharp changes with time that are difficult to explain or model. Their data indicate that the Pub 67 model probably overestimates the rate of urinary excretion of ^{241}Am at times remote from exposure, although perhaps not as much as suggested by Malátová et al (2010).

Malátová and coworkers assigned uncertainties in terms of "scattering factors" (as defined by Marsh et al. 2007) of 1.36 for U, and 1.31 and 1.37 for S for known and unknown head size, respectively. The scattering factors assigned to S were based on consideration of uncertainties associated with measurement error, reproducibility of the detector position, activity distribution in the skull, Monte Carlo simulations, and the percentage of skeletal Am in the skull. The scattering factors assigned to estimates of skeletal ^{241}Am may overstate their reliability, considering the sparsity of information on the portion of skeletal Am in the skull at any given time or age following intake of ^{241}Am. Malátová et al. (2010) assumed the skull contains 12.5% of skeletal Am based on autopsy measurements of ^{241}Am in four subjects (Lynch et al., 1989): three Pu workers with relatively low skeletal ^{241}Am (3.3, 5.3, and 12.4 Bq), and a chemist with a skeletal ^{241}Am burden of 4400 Bq at 25 y after apparent exposure via a wound to relatively pure ^{241}Am (USTUR Case 102, discussed earlier). The skeletal distribution of ^{241}Am in the three Pu workers may be more indicative of the systemic biokinetics of Pu than that of Am. As indicated earlier, Am has a greater affinity than Pu for cortical bone, the dominant bone type in the skull. The estimated percentage of skeletal ^{241}Am in the skull of the fourth subject was only moderately higher than the values for the Pu workers, but this subject had an unusually large portion of bone mineral in his lower body. Durbin and Schmidt (1985) extrapolated the findings for this subject to a skull content of 17.9% of skeletal Am in an age-matched adult with a typical distribution of bone mineral.

We examined whether there was a typical pattern of change over time in 24-h urinary ^{241}Am in individual subjects of Malátová et al. (2010) that were followed for at least 5 y. We also compared the time-dependent urinary ^{241}Am patterns for individual subjects with model-

generated values normalized to earliest urinary ^{241}Am measurements for each subject. The results of the analysis were found to be relatively insensitive to the time-course of absorption of ^{241}Am to blood, provided absorption was largely complete by the beginning of urinary ^{241}Am measurements. For simplicity, the model-generated urinary excretion curves were based on injection of ^{241}Am into blood at the time of exposure assigned by Malátová and coworkers. For a specific subject, the injected amount was set to reproduce the observed mean rate of urinary excretion of ^{241}Am at the earliest time of measurement over at least three consecutive days. For example, the earliest set of 24-h measurements of urinary ^{241}Am over three consecutive days for Subject JH were 43.9, 35.1, and 36.7 mBq d^{-1} on days 8994-8996 post intake, so JH's intake was set to yield urinary ^{241}Am of 38.6 mBq d^{-1} (the mean of the three observed values) on day 8995. As seen in Figure 3, the model-generated curves do not closely reproduce the observed pattern of excretion over the entire study period for any one subject. It does not appear feasible to develop parameter values within the applied model structure that would yield substantially closer reproductions of the urinary excretion data for multiple subjects due to the large scatter in the data for individual subjects, the wide variation across subjects in excretion patterns, the non-monotonic trends of the data in some cases (most pronounced for FK and HV), and the sharp declines in the excretion rates in other cases (most pronounced for JH at ~11,500 d and PV between 8500 and 8800 d). The increasing excretion rates at late times in some subjects may reflect increasing rates of bone loss in those subjects. The sharp declines in excretion rates at late times in other subjects are more difficult to explain.

Table 4 compares model simulations of the ratio U:S (defined above) with observations of Malátová et al. (2010), i.e., values derived from the measured activity in urine and the skull. Extrapolation of measured ^{241}Am in the skull to total skeletal ^{241}Am (S) is based here on the assumption that the skull contains 17.9% of skeletal ^{241}Am. The observations are grouped within 500-d periods post exposure starting at 4000 d, approximately the shortest observation time since exposure for any of the subjects. The ratio U:S for a given subject and 500-d interval was based on the mean urinary ^{241}Am value for that interval, divided by an estimate of the skeletal ^{241}Am for that subject at the mean measurement time within the interval. Skeletal activity $S_X(t)$ for Subject X at a given time t was derived from an exponential function $S_X(t) = ae^{-\lambda t}$ derived as a least-squares fit to the estimates of skeletal ^{241}Am over Subject X's entire observation period. Model simulations were based on injection of ^{241}Am into blood at time zero. The results shown in Table 4 were found to be virtually unchanged by assuming instead that the subjects inhaled a moderately soluble form of ^{241}Am, as was assumed in dose reconstructions for these subjects reported by Malátová et al. (2003).

As seen in Table 4, the Pub. 67 model overestimates the observed mean ratio U:S during all 500-d intervals. Ratios U:S generated by the updated model are reasonably consistent with the mean M of observed ratios through about 8500 d post exposure but overestimate M thereafter. It was not feasible to derive parameter values that yield a good fit to M over the entire observation period due to sharp drops in M after the intervals 8000-8500 d and 10,000-10,500 d, which we not expect to represent typical Am kinetics at late times. These sharp declines may be an artefact of the changing composition of the study group when defined in terms of measurement times post exposure as estimated by Malátová et al. A sharp drop in the mean ratio at about 8500 d results from the entry into the study group of the subject with the lowest overall ratios U:S (Subject JH), together with sharp drops at roughly 8500 d in the urinary excretion rates of two other subjects (PP and PV). The mean ratio subsequently remains relatively steady until 10,500 d post exposure, when another sharp drop results from the exit

of two of the three remaining subjects, leaving only Subject JH. I

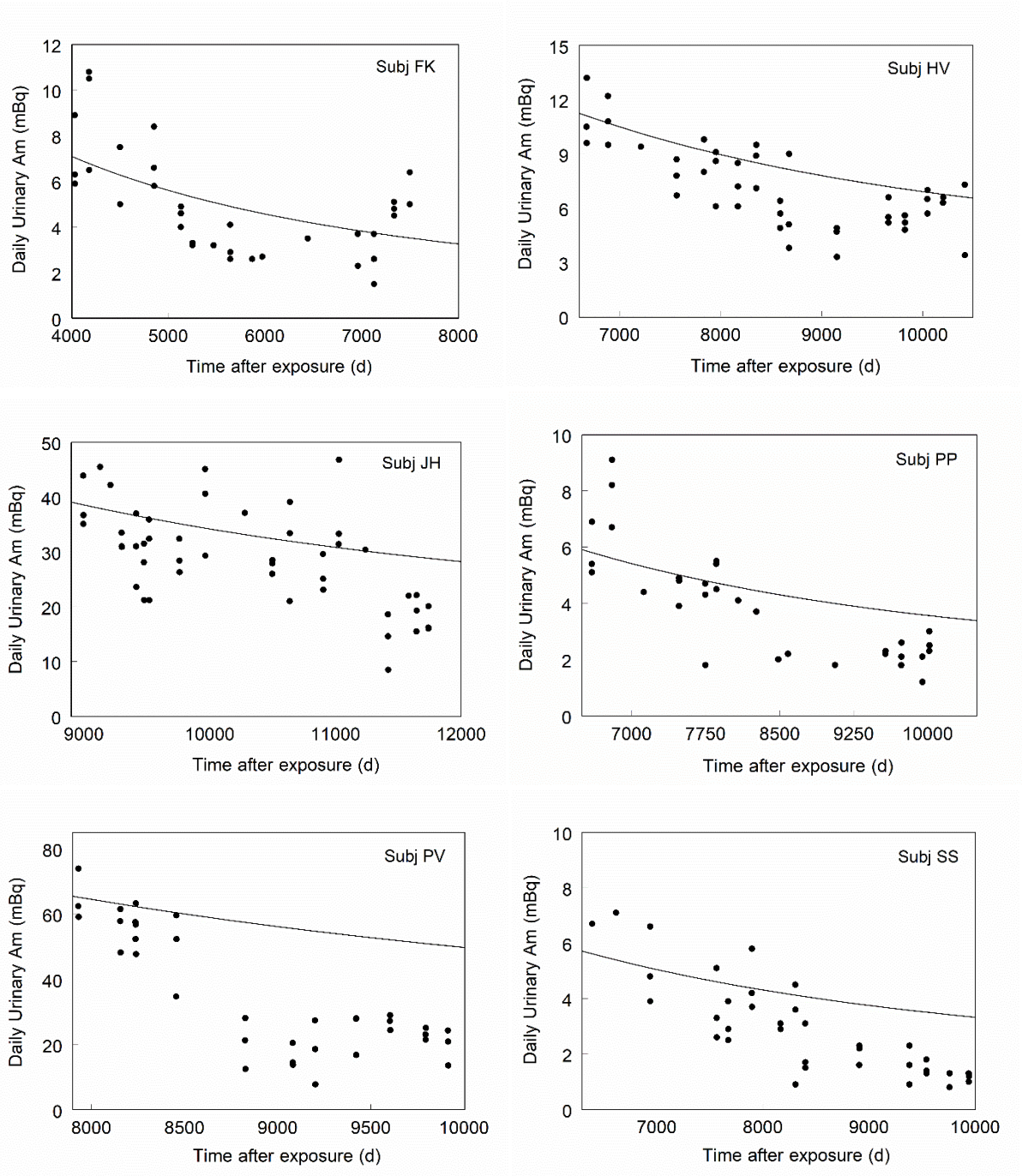

Figure 3. Comparison of observed and modelled pattern of change over time in urinary ^{241}Am. For each subject the model predictions are normalized to early observations, as described in the text.

Table 4. Observations and model predictions of the ratio of 24-h ^{241}Am in urine to ^{241}Am in skeleton based on external measurement in the skull[a,b].

Estimated time after exposure (d)	n	Mean ratio × 10^{-5}	Range of ratios × 10^{-5}	Model predictions (×10^{-5})	
				Pub. 67	This update
4000-4500	1	3.3	-	4.5	3.4
4500-5000	1	2.7	-	4.2	3.0
5000-5500	1	1.5	-	4.0	2.8
5500-6000	1	1.2	-	3.8	2.5
6000-6500	2	2.3	1.4-3.1	3.6	2.3
6500-7000	4	2.2	1.2-2.7	3.5	2.1
7000-7500	3	1.8	1.4-2.3	3.4	2.0
7500-8000	4	1.8	1.3-2.0	3.3	1.8
8000-8500	4	1.5	1.0-1.9	3.2	1.7
8500-9000	5	0.9	0.7-1.4	3.1	1.6
9000-9500	6	0.9	0.6-1.4	3.1	1.5
9500-10000	5	0.8	0.6-1.3	3.0	1.5
10000-10500	3	0.9	0.5-1.4	3.0	1.4
10500-11000	1	0.53	-	2.9	1.3
11000-11500	1	0.49	-	2.9	1.3
11500-12000	1	0.36	-	2.8	1.2

[a]See text for method of calculation of ratios for individual subjects over 500-d periods.
[b]Skeletal ^{241}Am based on assumption of 17.9% of skeletal ^{241}Am in skull.

Summary and conclusions

The ICRP's current biokinetic model describing the systemic behaviour of Am in workers was developed in the early 1990s (Leggett 1992) and adopted by the ICRP in Publication 67 (1993), which addressed doses to members of the public from intake of radionuclides. The same model with parameter values restricted to an adult member of the public has since been applied in ICRP reports addressing occupational intake of Am (ICRP 1994, 1997).

Much additional information is now available on the systemic behaviour of Am, including long-term measurements of retention and excretion of ^{241}Am in many radiation workers and the post-mortem distribution of ^{241}Am in several workers. The Pub. 67 model for systemic Am appears reasonably consistent with the updated information with the main exception that two studies on workers exposed to ^{241}Am or its parent ^{241}Pu suggest that the model overestimates daily urinary Am at late times post exposure. Although the results of both studies involve sizable uncertainties regarding the typical systemic behaviour of internally deposited Am, it is concluded that they nonetheless indicate that the Pub. 67 model for systemic Am overestimates the Am excretion rate at late times after its uptake to blood.

The Pub. 67 model for systemic Am in adults was modified to yield lower urinary and faecal excretion rates at times remote from exposure. A few other modifications of that model were made to conform to default model structures and parameter values used in updated models for actinide and lanthanide elements (ICRP 2019, to appear). The following changes to the Pub. 67 model were made:

- The number of liver compartments was increased from one to two for consistency with the generic structure for the liver applied to actinide and lanthanide elements in OIR Part 4 (ICRP 2019, to appear). A biological half-time of 30 d was assigned to the fast-turnover liver compartment. A removal half-time of 1 y, the half-time applied to the single liver compartment in the Pub. 67 model, was applied in the revised model to the liver compartment with relatively slow turnover.
- The removal half-time from gonads was reduced from 10 y to 5 y, a generic value applied in the OIR reports to the actinides and lanthanides.
- A fraction F of Am removed from cortical bone was assumed to be locally recycled, i.e., redeposited on cortical surface after removal from cortical bone surface to cortical bone marrow by bone remodelling. The fraction 1-F was assumed to transfer from cortical bone marrow to blood. A local recycling fraction F=2/3 was selected for broad consistency with reported data on the long-term relation of ^{241}Am in bone and urinary ^{241}Am, taking account of limitations in the reported data.

Compared with the Pub. 67 model for systemic Am, the updated model predicts about a 25% increase in the number of nuclear transformations (nnts) on cortical bone surfaces of a worker over a 50-y period after acute input of ^{241}Am to blood; about a 15% decrease in nnts in kidneys, liver, and red marrow; and about a 50% decrease in nnts in gonads. Similar numerical changes are seen in derived 50-y committed equivalent doses to these tissues if a common dosimetry system is applied together with each of the alternate systemic models. When used for interpretation of observed urinary excretion of ^{241}Am, the updated model predicts a higher intake than does the model of Pub. 67, with the difference depending on the time after exposure and the time course of entry of ^{241}Am into blood.

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