Development of an Age- and Gender-specific Model for Strontium Metabolism in Humans

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Abstract. This paper presents a development of a new biokinetic model for strontium, which accounts for age and gender differences of metabolism in humans. This model was developed based on the long-term follow-up of the residents living on the banks of the Techa River (Southern Urals, Russia) contaminated with $^{89,90}$Sr in 1950-1956. The new model uses the structure of ICRP model for strontium but model parameters have been estimated to account for age, gender and population differences in strontium retention and elimination. Estimates of age- and gender-specific model parameters were derived from (a) the results of long-term measurements of $^{90}$Sr-body burden for the Techa River population; (b) experimental studies of calcium and strontium metabolism in humans and (c) non-radiological data regarding bone metabolism (mineral content of the body, bone turnover, etc). As a result, the new model satisfactorily describes data on long-term retention of $^{90}$Sr in residents of the Techa River settlements of all ages and both genders and also data from studies during the period of global fallout in the UK and the USA and experimental data on strontium retention in humans. The new model can be used to calculate dose from $^{89,90}$Sr for the Techa River residents and also for other populations with similar parameters of skeletal maturation and involution.

1. Introduction

$^{90}$Sr was widely dispersed in the 1950s and 1960s in fallout from atmospheric testing of nuclear weapons; the worldwide cumulative deposition of $^{90}$Sr peaked at about 500 PBq in 1966 [1]. The accident at the Chernobyl nuclear power plant in 1986 also introduced about 125 PBq of $^{89,90}$Sr into the environment [1]. Mayak Production Association, the first Russian site for the production and separation of plutonium, released about 21 PBq of $^{89,90}$Sr into the Techa River with peak amounts in 1950-1951 [2]. The contaminated water was the main source of drinking water for the Techa riverside residents. $^{90}$Sr was the most important source of internal dose for the population. Average $^{90}$Sr intake for adult resident in mid-Techa was about 3,000 kBq. The affected people have been followed for many years by physicians and scientists from the Urals Research Centre for Radiation Medicine (URCRM). The results of long-term dosimetric studies of the exposed population have been compiled into a special URCRM database. This database includes measurements of $^{90}$Sr content in bones, teeth and in vivo measurements of $^{90}$Sr-body burden with the use of a specially designed whole body counter (WBC) [3]. WBC measurements have been performed during 1974-1997 for more than 15,000 persons [4]. This data set is considered to be the largest of its kind in the world and can be used for studying strontium metabolism in humans. Analysis of WBC data on long-term $^{90}$Sr retention in residents of the Techa River settlements has shown evident differences in $^{90}$Sr-body burden in men and women [3, 5]. These differences are explained by features of bone mineral turnover, which is influenced by the process of sexual maturation in adolescents and reduced sexual functions in aging persons [5]. The model that is generally used for strontium biokinetics is that of the International Commission on Radiological Protection given in Publication 67 (ICRP67) [6]. However, the ICRP67 model is not gender specific. Furthermore, the ICRP67 model predictions were found to be higher than average WBC data on long-term $^{90}$Sr retention for persons aged 15-20 at the onset of intake, and lower for children aged 1-5 at the onset of intake [7]. To develop a more accurate model to describe strontium retention in males and females of all ages many data sets have been assembled. These data include WBC measurements of $^{90}$Sr-body burden for residents of the Techa River settlements and also data from studies during the period of global fallout, experimental data on retention of strontium radionuclides, and non-radiological data regarding bone metabolism.

2. Model Description

The structure of the new model (Techa Biokinetic Model, TBM) is shown in Fig. 1. As can be seen, the structure of the systemic model is similar to that of ICRP67 for strontium [6]; the kinetics of strontium in the gastrointestinal tract (GIT) is described by a four-compartmental model as in ICRP
Publication 30 [8]. Model parameters represent biological transfer rates (describe the fractional flow per unit time) between model compartments and are shown by arrows in Fig. 1.

Model compartments have the same anatomical and physiological interpretation as in ICRP models [6, 8] and are not described in this paper.

3. Model parameters estimation

The ICRP model for strontium accounts for age differences in metabolism and model parameters are estimated for basic referent ages: 3-mo infant; 1-year (y), 5-y, 10-y, and 15-y children; and adults. A linear interpolation of model parameters between referent ages is used to derive parameters for intermediate ages. Gender differences in strontium kinetics are not addressed in the model.

Parameters of the new TBM model were estimated for males and females for each age, from birth till 80 y old, and are accounted specifically for population age of sexual maturation (which determine the peak of strontium retention in the skeleton) and age-dependent bone loss in aging persons. Basic model parameters that account for age- and gender-specific features in strontium metabolism are as follows (shown by bold arrows in Fig.1): (a) calcium content in the skeleton and, as a derivation, calcium-accretion rate during skeletal growth and calcium loss in aging persons, which is used to evaluate transfer parameters ‘Plasma→Bone Surfaces’; (b) strontium elimination from deep bone volume, ‘Deep CV→Plasma and Deep TV→Plasma’, determined by cortical and trabecular bone turnover rates; (c) gastrointestinal strontium absorption used to evaluate parameter, describing the transfer ‘Small Intestine→Plasma’.

To develop the TBM model for strontium three major steps were followed: (1) derivation of specific model parameters based on available data on strontium, calcium and bone metabolism; (2) estimation of model parameters by fit to the major data sets on ⁹⁰Sr in humans; and (3) model validation by comparison of model calculations with data sets that were not used to estimate model parameters.
### 3.1. Derivation of model parameters using literature data and WBC measurements for the Techa River population

#### 3.1.1. Age- and gender-specific calcium content in the skeleton for the Urals population

An age-dependent function describing changes of calcium content in the skeleton through human life is used in ICRP models for earth alkaline elements to derive fractional deposition of the elements on trabecular and cortical bone. This function was obtained using autopsy measurements of calcium content in the skeleton for boys aged between 5 and 17 years and radiographic measurements of relative changes in skeletal mass with age [9].

Extensive data sets on mineral content of the body have been obtained in recent years with the use of dual photon absorptiometry (DPA) and dual energy x-ray absorptiometry (DXA). Analysis of these data shows the following features of calcium gain and loss in the skeleton that should be taken into consideration: (a) most skeletal growth and mineralization occurs during the first two decades of life until the bone mass reaches its peak value at skeletal maturity, and then it remains relatively stable (the period of ‘plateau’ in bone mass); (b) for women, the ‘plateau’ extends until pre-menopause; after which a rather rapid bone loss occurs; (c) for aging men, the loss of bone mineral is less pronounced; and (d) there is a significant gender and ethnic difference in value of peak bone mass. These gender and ethnic differences in bone mineral content should be taken into account to develop a population-specific biokinetic model for strontium. Therefore, it is important to revise the age-dependent function of calcium content in the skeleton accepted in ICRP67 and evaluate age- and gender-dependent changes of calcium in the skeleton specifically for the population of the Techa River settlements.

Residents of the Techa River settlements are representatives of the rural Urals population comprised mainly of Russians and Tatar-Bashkirs. Measurements of calcium content in the body have not been conducted for residents of the Urals; estimates of calcium content in the skeleton have been based on literature data and some assumptions applied to periods of skeletal development through the entire life: newborns and children – adolescents – adults – aging persons.

Data on chemical analysis of autopsy samples on calcium content in the skeleton of Russian newborns were used as an estimate of calcium content for newborns independent of gender (Table I) [10]. Calcium accretion rate in the skeleton of children before puberty is assumed to be independent of gender and is close to values estimated in [9].

The rate of calcium accretion in adolescents is dependent on skeleton development during puberty. As shown by numerous studies, the maximum rates of height growth and of calcium accretion occur prior to puberty and are associated with the age of menarche for girls and the period of sexual maturation for boys [11, 12]. The pattern of growth in boys differs from girls: boys have two more years of pre-pubertal growth because of the later onset of puberty and their pubertal growth spurt lasts for 4 years compared to 3 years for girls [13]. The age at which pubertal development occurs is different in different populations. Also, there is a secular trend of a decrease in the age of pubertal development, especially for urban populations. For the Techa River residents, the average age of menarche for girls in the 1950s was 15.3 y [5]. For comparison, the average age of menarche for girls in the 1970s in Russia was 13 y [14]. Therefore, estimates of calcium accretion rates should be accounted for features of sexual maturation of the population being considered. For the TBM the age-dependent retention of strontium at long times after intake, evaluated using WBC data, can be used to evaluate the location of age peaks in calcium accretion for girls and boys (residents of the Techa Riverside settlements).

Data from chemical analysis of calcium content in the skeleton of adult Russian women, presented in Table I [10], were used as an estimate of the reference level of calcium content in women of the Urals population during the period of stable bone mass (the ‘plateau’). To evaluate the calcium content in men of ‘plateau’ age a ratio of 0.76 [15] between bone mass of women and men of ‘plateau’ age was used. As can be seen from Table I the reference parameters adopted for Asian Reference Man [15] are closer to the Urals population than those of ICRP70 [16].
For the TBM model it is assumed that bone mass for women remains stable until the age of 45 y (pre-
menopause); for men, the period of the stable bone mass is assumed to occur until 55 y [17]. It is
assumed that calcium loss occurs exponentially in women [18] and occurs linearly in men [19].
Comparison of the accepted calcium content in the skeleton for the Techa River population with
available data on DEXA measurements showed that estimates of calcium content in the skeleton are
consistent with experimental data.

Table I. Measurements of calcium content in the skeleton for adults and newborns.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Newborn</td>
<td>27.3±5.9</td>
<td>28</td>
<td>–</td>
</tr>
<tr>
<td>Adult woman</td>
<td>732±24</td>
<td>860</td>
<td>715</td>
</tr>
<tr>
<td>Adult man</td>
<td>960*</td>
<td>1180</td>
<td>940</td>
</tr>
</tbody>
</table>

*Calculated in this study as applied to Urals population based on measurements of Borisov [10] for adult women

Following the assumption made for the ICRP67 model and extended above for the TBM, the rate of
calcium accretion is proportional to age- and gender-dependent changes in the model parameters:
Plasma $\rightarrow$ Trabecular Surface and Plasma $\rightarrow$ Cortical Surface.

3.1.2. Age and gender-specific strontium elimination from deep bone volume

Age- and gender-dependent rates of strontium removal from deep bone volume are assumed to occur
only by turnover of trabecular and cortical bone. Values adopted by ICRP are mainly based on the
results of histological studies and assessments of turnover rates using data from studies of global
fallout [16]. Analysis of these data shows that they cannot be used for accurate age- and gender-
dependent assessments of bone turnover rates. For the TBM the estimates of cortical bone turnover
rates for adult (aged 25-80 y) men and women were obtained using repeated WBC measurements for
the Techa River population. As discussed in [17], the rates of strontium elimination from the skeleton
estimated for the Techa River residents at long times after the intake reflect age and gender
dependencies of cortical bone remodelling rate. It was shown that strontium elimination rates remain
constant for women aged 25-45 y and for men aged 25-55 y. An increase in strontium removal from
the skeleton was observed for women in pre-menopause (after 45 y) and in aging men (after 55 y)
[17]. In order to obtain a continuous function describing rates of the cortical remodelling for aging
persons, a linear regression of averaged age-grouped strontium elimination rates was used. Fig. 2
shows average age-grouped values of strontium elimination rates based on WBC data for the Techa
River residents and estimates of the TBM parameter of strontium removal from deep cortical bone.

![FIG. 2. Age-related changes in mean values of strontium removal from deep cortical volume for
men and women (points) and assessments used in TBM (lines). The bars indicate standard errors of
mean.](image)

For the TBM the trabecular bone turnover rate (Deep TV $\rightarrow$ Plasma) for adults was evaluated as a
product of the value for cortical bone and a ratio between remodelling rates for trabecular and cortical
bones [16], which is equal to six. Estimates shown in Fig. 2 are in agreement with qualitative
information obtained with new methods using biochemical markers of bone turnover.
Information on biochemical markers can also be used to evaluate relative dynamics in bone formation and bone resorption for children and adolescents. The changes in bone formation and resorption can be characterized as follows: (1) the maximal rate of bone turnover is observed in newborns; (2) then, a significant drop in the rate occurs to the ages of 3–5 y; (3) the rate then remains relatively stable until the start of sexual maturation (puberty), (4) an increase occurs during puberty with the increase for boys delayed by 2–3 y compared to girls; (5) the rate of remodelling then decreases significantly with age until the adult value is reached.

Analysis of other literature data for children and adolescents including histological methods and estimates derived from studies of global fallout shows that expert estimates of the rates of bone deposition and resorption can vary over a large range. Final estimates of gender-specific bone-turnover rates for children and adolescents can be obtained by determining the values of these parameters by fitting the model to data on $^{90}$Sr-body burden in humans.

3.1.3. Age- and gender-specific gastrointestinal absorption of strontium ($f_1$ factor)

Strontium is relatively well absorbed in the GI tract although discrimination exists against strontium absorption comparing to that of calcium at all ages except infants [20]. The ICRP67 model does not address discrimination between calcium and strontium absorption in the GIT; therefore, the $f_1$ factor should be reconsidered taking into account age, gender and population features. Analysis of literature data on strontium absorption in humans indicates that such studies have been made only for adults and the reported range of gut absorption extends from 0.103 to 0.534 [21]. According to [22], the distribution of values may be approximated as a lognormal distribution. By assuming that the ends of the reported range of strontium-absorption values indicated above are the 1st and 99th percentiles of a lognormal distribution, a geometric mean value for adults of ‘plateau’ period is 0.235. It is assumed here that the age dependence of strontium absorption for children and adolescents and for aging persons is quantitatively the same as for calcium, which is studied more extensively. Fig. 3 shows experimental data on the absorption of calcium and strontium and the expert assessments of strontium absorption in the GIT reported in ICRP Publications 56 and 67 [23, 6] in comparison with the values of strontium absorption in the GIT for males and females aged from birth till 80 y used for the TBM.

![Graph showing age- and gender-specific values of strontium and calcium absorption in the GIT for males and females.](image)

**FIG. 3.** Age- and gender-specific values of strontium and calcium absorption in the GIT for males (a) and females (b). Experimental data on calcium and strontium absorption are compared with the ICRP67 [6] and ICRP56 [23] assessments and the gender-specific values that used in the TBM.

3.2. Estimation of model parameters by fitting model calculations to data on $^{90}$Sr content in humans

The solution of the system of linear differential equations for the TBM was obtained numerically with the use of the fourth order Runge-Kutta method. The computer code developed for this purpose was tested by using the parameter values reported by ICRP67. Once the code was developed, model parameters, which were not evaluated on the basis of literature data, were estimated by fitting model
predictions to data on $^{90}\text{Sr}$ content in humans. Three major data sets on measured $^{90}\text{Sr}$-body burdens were used to fit age- and gender-dependent model parameters, including

“Techa River data” – WBC measurements of $^{90}\text{Sr}$-body burdens conducted for the permanent residents of Muslyumovo settlement located on the Techa River. This data set represents measurements for both genders of all ages from birth till 50-y old at intake for a homogenous population with homogenous intake. For the purpose of model-parameter estimation, two cuts of age- and gender-dependent WBC measurements were estimated: (a) age- and gender-dependent $^{90}\text{Sr}$-body burdens 30 y after intake (1980) and (b) age- and gender-dependent $^{90}\text{Sr}$-body burdens 45 y after intake (1995).

“UK global fallout data” – Radiochemical measurements of $^{90}\text{Sr}$ concentration in femur conducted in the UK in 1964 [24]. This data set includes measurements of $^{90}\text{Sr}$ in femur bone normalized on calcium content for ages from birth till adulthood and is not separated by gender. Therefore, as there is no difference in calcium and strontium metabolism between boys and girls and there is no significant difference in calcium concentration in skeleton between ethnic groups before pubertal development, this data set can be used for fitting model parameters for girls and boys before puberty (0-9 y).

“US global fallout data” – Radiochemical measurements of $^{90}\text{Sr}$ concentration in vertebrae conducted in San Francisco in 1964 [9]. This data set is similar in character to the UK data set.

3.2.1. Evaluation of parameters for adults

For the TBM, “adulthood” is considered separately for two periods in human life: (1) stabilization of mineral-turnover rates, when the calcium content in the skeleton is constant (‘plateau’ period); and (2) the involution of the skeleton, when bone-mineral loss occurs.

The first period occurs from the age of 25 y until 55 y for men and 45 y for women. During the first period the TBM parameters remain constant. No gender differences in parameters are assumed except for removal rates from deep bone volume. Age and gender dependencies of calcium content in the skeleton, and rates of bone turnover were used to derive model parameters for the TBM that describe strontium deposition on bone surfaces and strontium removal from deep bone volume. Other model parameters were derived by fitting model calculations performed on the basis of intake of $^{90}\text{Sr}$ by residents of Muslyumovo [25] to the results of WBC measurements (“Techa River data”) or were adopted from ICRP67 model for strontium [6].

The second period starts from 55 y for men and 45 y for women. For this age period it is assumed that age- and gender-dependent deposition of strontium on bone surfaces decreases proportional to calcium loss in the skeleton. Deposition in soft tissues and excretion pathways are assumed to increase due to competition with skeleton and are estimated based on balance equation. Age- and gender-dependent bone turnover rates increase indicating bone mineral loss during involution of the skeleton. Strontium absorption in GIT declines both in men and women. Other parameters are independent of age and are assigned to be the same as for ‘plateau’ period.

3.2.2. Evaluation of parameters for adolescents and children

As described previously, parameters of removal from deep bone volume were not accurately estimated based on literature data for ages from birth till 24 y. These parameters were evaluated by fitting model calculations to data on measured $^{90}\text{Sr}$ in humans. Other parameters were evaluated based on balance equations; removal rates from bone surfaces were corrected for the age of sexual maturation. Parameters independent of age and gender were directly taken from ICRP67 model for strontium [6]. No gender differences in model parameters are assumed for ages 0-9 y.

As described, WBC data for Muslyumovo residents and data from global fallout obtained in 1964 were used to fit model parameters. These three sets of data supplement each other. The “Techa River data” represent long-term retention of $^{90}\text{Sr}$ in skeletons of men and women, who were children and adolescents during the period of major intake (30–45 y ago). The most attractive feature of this unique data set is the precise identification of sharp gender-specific peaks in $^{90}\text{Sr}$ retention during puberty. The most attractive feature of the US and UK data sets on $^{90}\text{Sr}$ from global fallout is that these data include $^{90}\text{Sr}$ concentration in different bone samples measured during the period of intake for young children. The “UK global fallout” data set was used for fitting model predictions to average-$^{90}\text{Sr}$ concentrations with the assumption that the femur can serve as a surrogate for the skeleton. The “US
global fallout” data set was used for fitting model parameters to the concentration of $^{90}$Sr in trabecular bone. An age-dependent intake function was used as reported in [25] for model calculations of $^{90}$Sr-body burden for the Techa River residents. For fitting model calculations using data on the concentration of $^{90}$Sr from global fallout in bones the intake functions reported in [9] were used.

As a result, a universal set of parameters for males and females of all ages from birth till 80 years old was evaluated. The results of model parameters estimation are shown in Fig. 4 in comparison with “age-dependent cuts” of the WBC data 30 y after intake for men and women, respectively. As can be seen from Fig. 4, the TBM model predictions are very close to the measured values and TBM satisfactorily describes gender-differences in peak $^{90}$Sr-retention and decrease in aging persons. ICRP67 model does not address differences in $^{90}$Sr retention in males and females and is shown both to under-predict and over-predict measured values. Fig. 5 shows measurements of $^{90}$Sr concentrations in bones for children compared to TBM and ICRP67 model predictions. The measurements are for $^{90}$Sr from global fallout and were conducted in the UK and the USA in 1964. As can be seen, the TBM satisfactorily describes $^{90}$Sr retention in different bones for children.

3.3. Validation of the model by comparison with data sets that were not used to estimate model parameters

A number of available data sets were used to compare model calculations with actual measurements of strontium radioisotopes in humans, including short-term retention of strontium isotopes in whole body, soft tissues, excretion with urine and faeces after single intake or intravenous injection mostly to adults, and also data on radiochemical measurements of current $^{90}$Sr concentration in human bones as a result of chronic $^{90}$Sr intake from global fallout in the USA and the UK. The results have shown that
the model satisfactorily describes retention of strontium for different situations: acute and chronic exposure. In this paper, two examples of the validation of our new model are presented using data on accidental $^{90}$Sr uptake in man after contamination of the Techa River. The data are for residents of two settlements located on the Techa River: Metlino (in the upper Techa, was evacuated in 1956) and Muslyumovo (in the middle Techa, not evacuated). The description of these data is given in Table II.

Table II. Description of data on accidental $^{90}$Sr residents of the Techa riverside settlements Metlino and Muslyumovo used to validate the TBM model.

<table>
<thead>
<tr>
<th>Data Set</th>
<th>Type of measurements</th>
<th>Type of $^{90}$Sr intake</th>
<th>Age at onset of $^{90}$Sr intake and gender</th>
<th>Period of measurements (years after onset of $^{90}$Sr intake)</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Metlino’</td>
<td>Radiometry and radiochemical measurements of $^{90}$Sr content in the skeleton</td>
<td>Chronic intake during 1950-1956</td>
<td>Adults (age of ‘plateau’), both genders</td>
<td>1951-1976 (1-26 y)</td>
</tr>
<tr>
<td>‘Muslyumovo’</td>
<td>Radiochemical measurements of $^{90}$Sr clearance with urine</td>
<td>Chronic intake during 1950-1979</td>
<td>Adults (age of ‘plateau’), both genders</td>
<td>1967-1979 (17-29 y)</td>
</tr>
</tbody>
</table>

As shown in Table II, two different data sets are available to compare model predictions with actual measurements of (a) $^{90}$Sr excreted in urine and (b) $^{90}$Sr in the skeleton. To perform model calculations for Metlino residents the function of $^{90}$Sr intake was used that had been estimated in [27]. Fig. 6 illustrates model predictions and measurements of $^{90}$Sr in the skeleton for Metlino residents. The results are shown not to contradict to each other. Fig. 7 shows the results of model calculations of $^{90}$Sr excretion with urine and measurements for Muslyumovo residents. The intake function was used as estimated in [25]. Fig. 7 shows good agreement between calculated and measured values.

Validation of the model was provided for different schedules of intake for different ages. The ability of a biokinetic model to satisfactorily describe different situations can serve as an implied warranty of the correctness of the model over a wide range of conditions. The TBM model was developed for the Techa River population and can be used to describe strontium retention in other populations characterised by similar features of pubertal maturation and aging. Also, the approaches to derivation of age- and gender-dependent model parameters developed in this study can be used in model fitting to data on other populations.
4. Conclusions

This paper describes an improved biokinetic model for strontium, which accounts for age- and gender-differences in strontium retention and elimination. The following age and gender-specific model parameters were evaluated using the available literature data and WBC measurements for the Techa River population: (1) calcium content in the skeleton; (2) strontium elimination from deep bone volume; and (3) gastrointestinal absorption of strontium. Other model parameters were estimated by fitting model calculations to WBC data on long-term $^{90}$Sr retention for residents of the Muslyumovo settlement located on the Techa River and radiochemical measurements of $^{90}$Sr concentration in different bones as a result of global fallout in the USA and the UK collected in 1964. As a result, a universal set of parameters for males and females of all ages from birth till 80 years old was obtained. The TBM was validated using different sets of data on strontium in humans including short-term retention after single intake as well as $^{90}$Sr retention during chronic ingestion. Comparison of model predictions with actual data on strontium measurements shows that the TBM satisfactorily describes strontium retention for different kinds of intake. In spite of the fact that the TBM was developed for the Techa River population, this model can be used to describe strontium retention in other populations having similar characteristics of pubertal maturation and aging (influencing calcium and strontium metabolism) as those for the Techa River population.

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6. References


