STRONTIUM BIOKINETIC MODEL FOR MOUSE-LIKE RODENT

Georgy Malinovsky, Ilia Yarmoshenko, Michael Zhukovsky

Institute of Industrial Ecology UB RAS, S. Kovalevskoy Str., 20, 620219, Ekaterinburg, Russia

Developed strontium biokinetic model for murine rodent represents modification of model for reference human with reduced number of compartments. Estimation of biokinetic parameters is based on published experimental data on strontium retention in body of laboratory mice and rats. Application of the model allows estimation of strontium distribution by organs and tissues both in the cases of acute and chronic exposure with dependence of strontium activity in organs on time.

1. Introduction.

Design of internal dose assessment approach for biota that takes into account non-uniform distribution of radionuclide in animal organs and tissues can be based on modification of appropriate models developed for humans. Key tasks of such approach development are as follow:

– to analyze the distribution of radionuclide in animal organs and tissues for accepted exposure situation,

– to assess values of coefficients that relate radionuclide activity to dose absorbed in organs and tissues.

One of the most significant radiation accidents in the human history was that appeared at Mayak nuclear plant in 1957, which resulted in radioactive contamination of large territory (East-Ural Radioactive Trace, EURT) [1,2,3]. Area of EURT was contaminated by a range of short and long-lived radioactive isotopes. Currently, after a considerable period of time after the accident, the main dose contributing radionuclide in EURT is ^{90}Sr, which is a bone-seeking element with slow excretion from the bone tissue. Non-human EURT biota has been studied for a long time and considerable amount of radiobiological data was accumulated as well as data on radiation exposure effects on mouse-like rodents population were collected. At the same time dosimetry of wild animals, particularly small mammals, was not paid enough attention.

For assessment of contemporary radiation exposure of non-human biota it is suggested to choose murine rodents as a group of representative species considering that mouse-like animals are ubiquitous and more studied comparing with other animals. Murine rodents do not directly correspond to Reference Rat suggested by ICRP. These animals have less body weight and dimensions, besides, analysis of published data presented bellow shows that mice have specific values of strontium retention in the body.

In this paper the analysis of dynamics of ^{90}Sr content in organs and tissues was carried out applying published data. Performed analysis allowed designing and verification of strontium biokinetic model for murine rodent.

2. Review and analysis of published data.

Developing of biokinetic model was based on published experimental data on strontium retention in skeleton of laboratory mice. The researches on strontium retention in wild animals were considered as

well, however the number of such data was insufficient. Searching of published data was carried out through specialized abstract databases and indexing resources such as PubMed, SinceDirect, Web of Sciences, E-library etc.

Results of experiments with laboratory mice and rats were analyzed, while data on other small mammals (rabbits and dogs) was not considered. When analyzing the published data particular attention was paid to dependence of strontium retention both in skeleton and whole body on time since beginning of exposure. Both acute injection and prolonged intake were investigated. Totally the list of publications used for combined analysis included more than twenty items [4-20].

Analysis of experimental data confirmed significant variability of parameters characterizing the strontium retention in organism of small mammals. This variability is noted in many studies in which the review of experimental data was carried out.

A wide range of values of strontium retention in the organism of laboratory mice and rats is shown on the Fig. 1, where the points represent experimental data of strontium retention with time after injection. In spite of high variability the dependence of strontium retention (R, %) on time (t, day) can be described by two-exponential function:

$$R = K_1 \exp(-\lambda_1 t) + K_2 \exp(-\lambda_2 t),$$

where K_1=67.8%; K_2=32.2%; λ_1=0.44 day^{-1}, λ_2=0.003 day^{-1}. Values of standard error for λ_1 and λ_2 coefficients were 0.13 and 0.002 respectively.

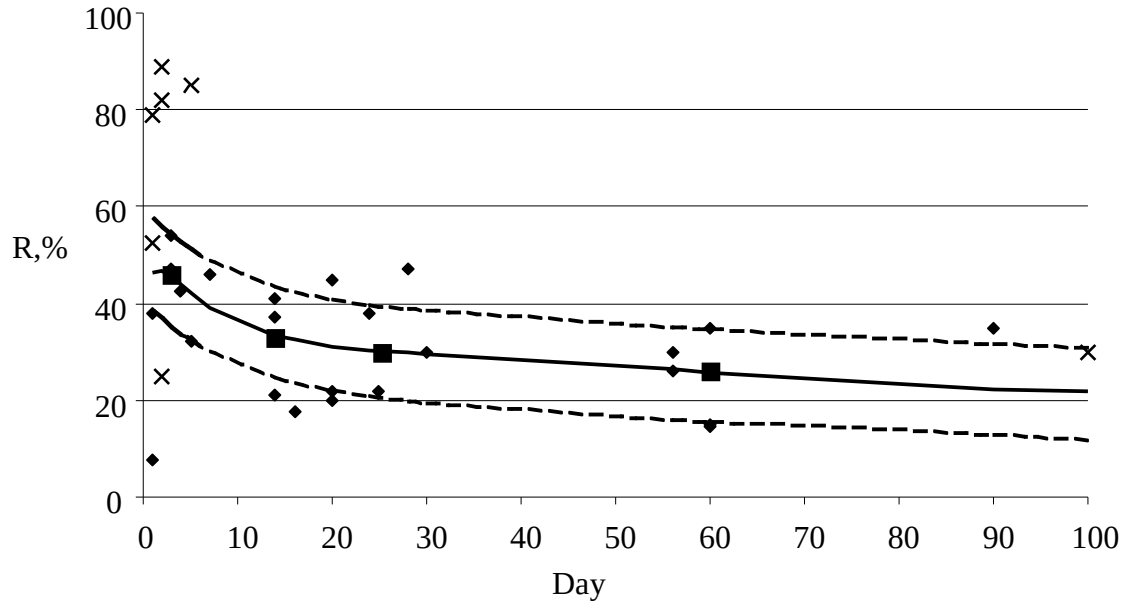

Fig. 1. Retention of strontium in skeleton of mice and rats with time since acute injection (% of intake). Diamonds – mice experimental data; crosses – rats experimental data; squares – referent values used for model validation; solid line – retention according to developed model with standard error (dash line).

Thus collected and analyzed data on intake and retention of strontium in body of laboratory mice allows estimation of coefficients included to strontium biokinetic model for murine rodent. The model can be verified using data on strontium retention after acute and chronic intake by requiring agreement of model retention to some ascertained reference values. The reference values of strontium retention in skeleton as follow were chosen: 46% by the end of third day, 33% on 14th day, 30% on 25th day and 26% on 60th day (Fig. 1).

3. Model development and coefficients assessment

For development of strontium biokinetic model for murine rodent the analogous ICRP model for human were used with some simplification. In particular the model was reduced by abandoning the division of gastrointestinal system into compartments and combining other soft tissues into single model organ. The skeleton is modeled by two compartments with slow and fast exchange rates.

Thus the model includes five compartments (Blood, Gastrointestinal tract, Soft tissues, Skeleton, Urinary bladder) and eleven transfer rates:

- to Blood from Gastrointestinal tract, Soft tissues, Skeleton (fast and slow components);
- from Blood to Soft tissues, Skeleton (fast and slow components), Gastrointestinal tract and Urinary bladder;
- excretion from Gastrointestinal tract to feces;
- excretion from Urinary bladder to urine.

The values of some transfer rates can be estimated using published data on strontium retention in body of laboratory mice. At the same time complete set of model coefficients couldn't be gained from experimental data. In this case the general agreement of order of magnitude and relation between coefficients with those of the human model is required.

Suggested biokinetic model is described by a system of eleven differential equations. To solve the system the computer code Winact developed for human biokinetic modeling was applied where input parameters are transfer rates and radionuclides' intake while output parameters are activity of the radionuclide in the ascertained compartments with time. The acute and chronic intake cases are provided for estimation.

The Table 1 contains a set of transfer rates which does result in required reference values of strontium retention. The parameters values are presented with minimal accuracy – one significant figure, considering large variability of experimental data. It is essential that tiny change of transfer rates presented in Table 1 results in unacceptable imbalancing and departure of strontium retention from the reference values.

Table 1. Transfer rates of developed Strontium biokinetic model for mouse-like rodent.

Organ donor ->Organ receiver	Value, day^{-1}	Similar value in human model
GIT->Blood	3.0E+00	2.57
Blood ->GIT	2.0E-01	5.25E-01
Blood ->Bone_1	4.0E+00	3.75
Bone_1 ->Blood	5.0E-01	
Blood ->Bone_2	1.0E+00	
Bone_2 ->Blood	6.0E-03	5.75E-04
Blood ->UBCont	2.0E+00	1.73
GIT ->Feces	3.0E+00	
Blood ->SoftT	4.0E+00	9
SoftT ->Blood	1.0E+00	2.62
UBCont ->Urine	4.0E+00	

The model designed using parameters mentioned in Table 1 describes the data on strontium retention in skeleton of murine rodents presented on Fig. 1 with standard error of 9.5% (Fig. 1). The values of strontium retention obtained with developed model in whole body, soft tissues and blood as well as total excretion with urine and feces are shown on the Fig. 2.

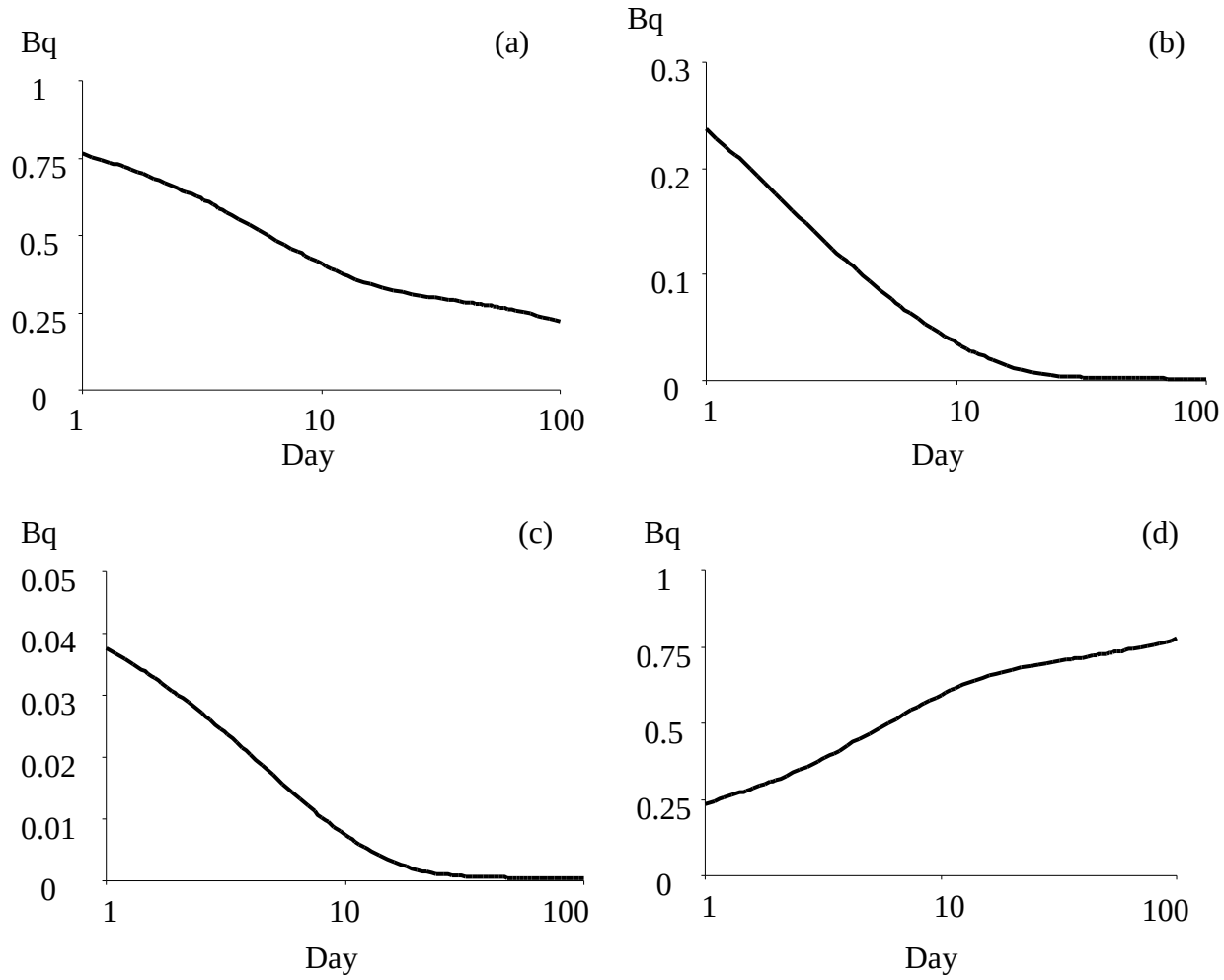

Fig. 2. Activity of strontium after 1 Bq injection a) in whole body, b) in soft tissues, c) in blood; d) total excretion.

Prolonged strontium intake was simulated under assumption of equality of transfer rates in the case of prolonged intake to those in the case of acute injection. This approach does not take into account the time variation of transfer rates e.g. with age of animal. Skeleton activity in the case of chronic exposure to 1 Bq per day is presented on Fig. 3a. As can be seen on Fig. 3a the skeleton activity rises approximately linearly during the first 100 days and accumulation reaches the factor of 14 and this value is in agreement with experimental data as well. Plateau of dependence of strontium retention in skeleton on time since beginning of exposure appears in 1000 days. It is essential that this value corresponds to life duration of murine rodents. As can be seen on Fig. 3b the daily excretion of strontium growths rapidly during first two weeks and than approaches gradually to value of daily intake.

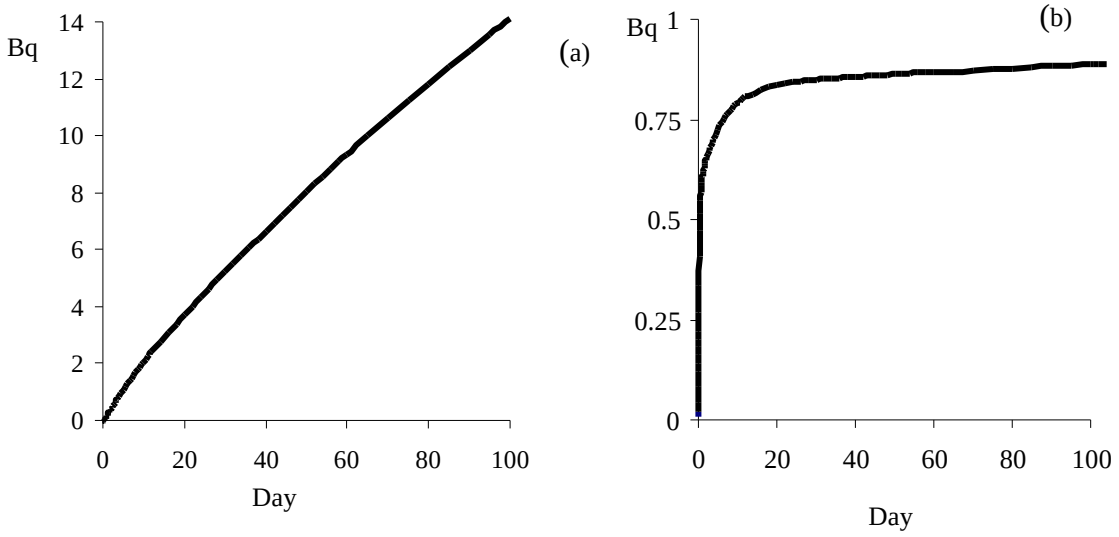

Fig. 3. Activity of skeleton (a) and daily excretion (b) in the case of chronic strontium intake.

4. Conclusion.

Developed strontium biolinetic model for murine rodent represents modification of model for reference human with reduced number of compartments. Application of the model allows estimation of strontium distribution by organs and tissues both in the cases of acute and chronic exposure with dependence of strontium activity in organs on time.

The model is based on published experimental data on strontium retention in body of laboratory mice and rats. Important feature of experimental data on acute injection consists in studying of strontium retention for the period of time that is compatible with life duration of the animals, i.e. the parameters of metabolism are changing during the experiment. Indeed, strontium is injected to young animals while the retention is measured in elder ones. Consequently the developed model is appropriate for the situation when the animal is rather young at beginning of exposure. At the same time there were no experimental data to estimate the strontium retention for newborn mice.

From radioecological point of view it is rather the strontium activity concentration in organs and tissues than whole body activity that is directly associated with absorbed dose. In order to estimate the concentration it is necessary to know whole body weight as well as organs' weights in dependence on age of the model animal. Considering constant chronic intake and weight increasing with age the activity concentration is not a linear function of strontium activity.

Developed strontium biokinetic model will be used for internal dose assessment for murine rodents inhabiting EURT territories. Comparison of dose estimations with studied effect of radiation exposure constitutes radiobiological basis for radiation protection of EURT biota.

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References

1. Kryshev I.I., Romanov G.N., Sazykina T.G., Isaeva L.N., Trabalka J.R., Blaylock B.G., 1998. Environmental contamination and assessment of doses from radiation releases in the Southern Urals. Health Physics, 74(6), 687–697.
2. Jones S., 2008. Windscale and Kyshtym: a double anniversary. Journal of Environmental Radioactivity, 99(1), 1–6.
3. Nikipelov B.V., Romanov G.N., Buldakov L.A., Babaev N.S., Kholina Y.B., Mikerin E.I., 1989. Accident in the Southern Urals on 29 September 1957. IAEA Information Circular 368. Report on a Radiological Accident in the Southern Urals on 29 September 1957. Vienna (IAEA).
4. Ray R.D., Thomson D.M., Wolff N.K., LaViolette D., 1956. Bone metabolism: II. Toxicity and Metabolism of Radioactive Strontium (Sr 90) in Rats. Journal of Bone and Joint Surgery, American Volume, 38, 160-174.
5. Starichenko V.I., Lyubashevsky N.M., Popov B.V., 1993. Individual variability of metabolism of osteotropic toxical substances. Ekaterinburg (Nauka), 165 p. (in Russian).
6. Cohn S.H., Lane W.B., Gong J.K., Weisbecker L., Milne W.L., 1957. Studies on the metabolism of inhaled aerosols of strontium and lanthanum. Research and Development Technical Report. U.S. naval radiological defense laboratory, San Francisco 24, California.
7. Synhaeve N., Stefani J., Tourlonias E., Dublineau I., Bertho J.-M., 2011. Biocinetics of ^{90}Sr after chronic ingestion in a juvenile and adult model. Radiation and Environmental Biophysics. 50, 501-511.
8. Takahashi S., Oghiso Y., Sato H., Kubota Y., 1989. The distribution and retention of ^{89}sr in mice after a single intravenous injection of high and low doses. Journal of Radiation Research, 30, 176-184.
9. Baryakhtar V.G., Bondarkov M.D., Gaschak S.P., Goryanaya Ju.A., Maximenko A.M., Liabik V.V., Chesser R.K., Baker R.G., 2003. Problems in small mammals radioecology. Environmental Science and Pollution Research. Special Issue, 1, 95–106.

10. Rönnbäck C., Nilsson A., 1975. The influence of oestrogen on the excretion of strontium-90 and -85 in mice. Acta Radiologica: Therapy, Physics, Biology, 14, 485-496.
11. Nilsson A., Bierke P., Walinder G., Broome-Karlsson A., 1980. Age and dose related carcinogenicity of ^{90}Sr Acta Radiologica Oncology, 19(3), 223-228.
12. Van Putten L.M., 1962. Treatment of radiostrontium intoxication in mice. I. The enhancement of elimination of radiostrontium International. Journal of Radiation Biology, 5(5), 471-476.
13. Volf V., Roth Z., 1966. Retention of strontium 85 in rats. III. Effect of increasing the doses of sodium and barium sulphates and role of the time factor. Acta Radiologica: Therapy, Physics, Biology, 4, 481-493.
14. Nelson A., Rönnbäck C., Rosén L., 1963. Further attempts to influence the elimination of radiostrontium. Acta Radiologica: Therapy, Physics, Biology, 1(3), 129-139.
15. Nilsson A., Rönnbäck C., 1988. Influence of low temperature on the excretion of radiocesium and radioruthenium compared with radiostrontium. Acta Oncologica, 27(3), 289-292.
16. Barmada R., Thompson D.M., Ray R.D., 1971. Mobilization of Strontium from the Rat Skeleton. Clinical Orthopaedics and Related Research, 79, 197-204.
17. Varga L.P., Sztanyik L.B., Rónai E., Bodó K., Brücher E., Györi B., Emri J., Kovács Z., 1994. Mobilization of radioactive strontium from mouse and rat using dicarboxylic acid derivatives of cryptand (2 .2). International Journal of Radiation Biology, 66(4), 399-405.
18. Cohn S.H., Baker D.G., Jahn A., Dombrowski C.S., 1969. Influence of cold exposure on skeletal metabolism in rats. Journal of applied physiology, 26(5), 524-529.
19. Rönnbäck C., 1986. Strontium retention in mouse foetuses at different intervals after contamination of the dam. Acta Radiologica Oncology, 25(2), 155-159.
20. Buldakov L.A., Moskalev Y.I. Problems of distribution and experimental assessment of Cs-137, Sr-90 and Ru-106 reference levels, 1968. Moscow (Atomizdat), 295 p. (in Russian).