International Research Journal of Biological Sciences _____ ISSN 2278-3202
Vol. **2(2),** 34-39, February **(2013)** *Int. Res. J. Biological Sci.*

A Radiation Carcinogenesis Model Applied to Radon- Induced Lung Cancer Risk Prediction Using a Sugarscape Cellular Automaton

Baradaran Samaneh[1], Setayeshi Saeed[1*], Maleknasr Niaz[2] and Kardan Mohammad R.[3]
[1]Department of Medical Radiation Engineering, Amirkabir University of Technology, Tehran, IRAN
[2]Faculty of Engineering, Science and Research Branch, Islamic Azad University, Tehran, IRAN
[3]Radiation Application School, Nuclear Sciences and Technology Research Institute, Tehran, IRAN

Available online at: www.isca.in
Received 18th November 2012, revised 29th November 2012, accepted 16th December 2012

Abstract

Exposure to Radon and its decay products is one of the important risks of ionizing radiation from natural sources. It is the second leading cause of lung cancer after smoking in the world. This special characteristic makes an increase in methods and models of lung cancer risk prediction from Radon. In this paper, we present a stochastic cellular automaton based on sugarscape to computational study complex biological effect of radon progeny alpha particles in lung bronchial airways. Our major objective is an assessment of lung cancer risk by following mechanism of cell action in different radiation doses. The model included mechanism of DNA damage induced alpha particles hits and formation of transformation in the lung cells. To achieve our goal, we follow the metabolism rate of infected cell induced alpha particles traversals in sugarscape environment to reach oncogenic transformation. For the first time, a cellular automata model is used to calculate transformation frequency in lung bronchial airways induced Radon and to predict lung cancer risk. The results are validated by a comparison epidemiological data, dosimetric and biological models. It has been shown that the cellular automata using sugarscape model could be a suitable method for cancer risk prediction.

Keywords: Sugarscape cellular automata, metabolism rate, oncogenic transformation, Radon progeny alpha particles, lung cancer risk.

Introduction

Radon is a natural radioactive gas with a half life of 3.8 days that decays into ^{218}Po and ^{214}Po progeny. They are electrically charged and can attach themselves to tiny dust particles in air and insert respiratory system. The ^{218}Po and ^{214}Po emit alpha particles with 6 and 7.6 MeV in respect, during their decay. They have been enough potential to damage lung cells. This DNA damage has the potential to malignant changes and lead cancer[1].

Evidence on Radon and lung cancer is now available from about many epidemiologic studies of underground miners and residential studies that provided quantitative information on the exposure-response relationship between Radon and lung-cancer risk[1-4].

Several approaches such as *empirical, dosimetric*, and *biological* have been designed to estimate lung cancer risk associated with Radon exposure.

In the *dosimetric* approach lung cancer risk is related to cellular doses in bronchial airways. The ICRP quantities (ICRP 1991) are used to estimate a bronchoepithelial dose per Jhm^{-3} (WLM) and convert that lung dose with appropriate factors. This approach is subject to major uncertainties[1,5].

The *empirical* approach would use the statistical methodologies to analyze epidemiologic data from miner and residential studies. This method employs a risk model based on the studies from three data sources (miner studies, domestic Radon exposure studies, and populations exposed to γ rays).

The *biological* approach uses data from molecular, cellular, and animal studies to produce parameters which could be used to follow carcinogenesis process. In this approach experimental data is sued to formulated molecular and cellular biological behavior after radiation exposure[1].

Recently, Transformation frequency- Tissue response (TF- TR), a mechanistic biology based model is designed to assess lung cancer risk induced Radon progeny alpha particles[6-8].

These approaches following estimation risk induced Radon are very costly, time consuming, and need to use some modern and complex techniques with a high uncertainty because of transferring parameters from in vivo to in vitro situations.

The cellular and molecular mechanisms for radon-induced carcinogenesis are not clear yet[9]. The complexity of carcinogenesis process and lack of experimental data for surveying and studying has led the scientists to take advantage of computational and modeling methods to predict, recognize and treat of this dreaded disease. Mathematical Formalism,

Artificial Intelligent and Artificial Life are some of the computational tools of predictive radiation biology. Cellular automaton is used as a one of the Artificial Life techniques to study and simulate phenomena of complex living systems.

Cellular automata enable by using cellular dynamics and including interaction between cells provide the suitable computational model for the study of complex system such as carcinogenesis process.

A cellular automaton is a collection of cells on a grid of specified shape that evolves through a number of discrete time steps according to a set of rules based on the states of neighboring cells. The rules are then applied iteratively for as many time steps as desired. Von Neumann was one of the first people to consider such a model, and incorporated a cellular model into his "universal constructor." Cellular automata were studied in the early 1950s as a possible model for biological systems[10]. A CA model is represented as a lattice or array of cells. The size of this lattice is referred to as the dimension of the CA. The characteristics of cellular automata are given in references[10-15].

The advantages of CA include taking into account the local interaction of alpha particles hits and cell infections.

In the present work a methodology based on a combination of cellular automata and sugarscape is proposed to predict lung cancer risk induced Radon progeny alpha particles.

Sugarscape was first introduced by Epstein and Axtell[15]. This environment is multi-agent system that used for modeling and organizing social, biological, political and economic process. The sugarscape environment is based on simplicity which means the rules in this environment are simplified[15].

Main elements of model are Cellular Automata (environment), agents, sugar (source) and rules[12-16].

Agents refer to the elements which live in the environment and have a set of properties that can change during time. Agents need to consume sugar for survival. Sugar is a generalized source which should be eaten by agents for survival. In this model agents are lung cells and sugar is glucose that is needed to consume for metabolism. Metabolism is one of the important biomarker to diagnosis cancerous cells. Enhanced of metabolism mechanism is happened during carcinogenesis process because of mutations in the mitochondrial DNA resulting in oncogenic transformation[17].

Metabolism as an important biomarker used in this model to follow states of damaged cells induced alpha particles hits to be oncogenic transformation state.

The objectives of the present work are i. to simulate the cellular state behavior induced by Radon progeny alpha particles hits, ii. to evaluate oncogenic transformation induced alpha particles hits iii. to compare the risk predictions with available risk data.

Material and Methods

The cellular sugarscape model was performed in Matlab using the 2 dimensional lattices. A square lattice of size L×L grids was used to present configuration in order to explain the changes in all cell stages in a lung tissue.

Initial healthy cells are randomly distributed across the sugarscape environment (lung tissue). Every cell has the amount of sugar which is randomly ranges from 0 to 1. Each site has the sugar level is uniformly (Gaussian) distributed between 0 and 1. At each timestep sugar level of the sites regenerate randomly.

The direct biological effect of ^{214}Po and ^{218}Po alpha particles which passed lung cells nucleus can be the oncogenic transformation.

Epidemiologic studies on lung cancer show that the number of cells hit is an important quantity to evaluate radiation biological effect. For this purpose considering the number of hits is necessary. From experimental data cellular hits by alpha particles is described by the Poisson distribution[7-8].

In this study, the average number of hits is calculated for different doses over 4 years exposure period, representing the average working exposure time for miners.

Alpha particle hits the normal cell, and this hits occurred with Poisson distribution as mentioned earlier. The state of each hit cell changes to infected cells. These infected cells collected the sugar from sites that they are located in and increment their sugar level. In the model, metabolism rate is used to determine cell state.

The meaning of each stage is defined as follows: Infected stage 1 (Landscape1): a cell that has been recently infected when cellular hit with alpha particles is occurred with the Poisson distribution. In this stage by considering dose and time of exposure, the mean number of hit is calculated and based on this parameter the actual number of hits in nucleus of lung basal or secretory cells is selected from Poisson distribution.

Infected stage 2 (L2): The infected cell has been already recognized. When alpha particles pass through the cell nuclei DNA, damage is happened and cell is initiated. The metabolism rate of these damaged cells has been increased because of their cell cycle is became shorter and their mitosis is occurred rapidly. Thus they need to receive more nutrients to upgrade their level to survive. They have to compete with each other to receive threshold nutrient to continue life. If the sugar level of cells is less than threshold its stage does not change. If cell's stage didn't change within 2 timestep, they become necroses and die.

Infected stage 3 (L3): The infected cell in this stage have received stage's sugar threshold. In this stage random Gaussian distribution of sugar is performed again. If the sugar wealth of cell is greater

than stage's threshold, increment of stage is occurred. If the sugar level of cells is less than threshold its stage does not change. If cell's stage didn't change within 2 timestep, they become necroses and die.

Transformants (T) (L4): the cells that reach this stage have the most metabolism rate and have maximum chance to be cancerous cells. In the highest level of metabolism (Landscape 4), model is convergence. The numbers of cells in this level are oncogenic transfomant cells induced alpha particle hits which they have the maximum chance to make tumor.

The model outlined above have been implemented according to 2 dimensional CA model based on the classic sugarscape model, which describe the evolution of alpha particles infection under different condition such as dose and time of exposure. The simulation flow chart of model is shown in figure-1.

We believe that cellular automata (CA) with carefully selected parameter values can obtain a clearer picture of the effects of Radon progeny alpha particles infection on the lung cells.

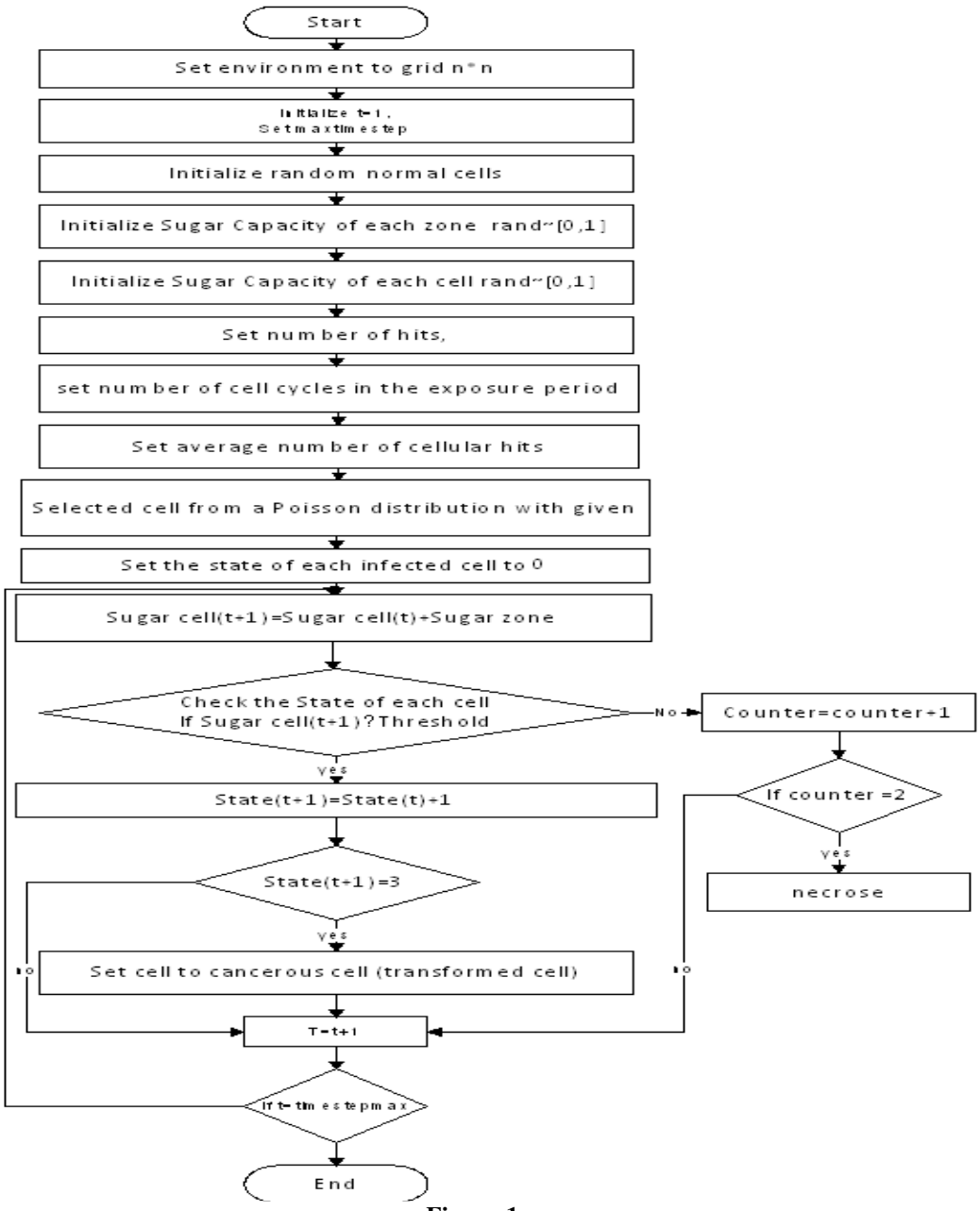

Figure-1
Flow chart describing transition between 4 infected cells stages

Results and Discussion

In this study, a stochastic CA model associated with the sugarscape environment is explored under various parameters and focused on the changes in metabolism rate due to DNA damage by Radon progeny alpha particles hits. The model determines the cellular hits with alpha particles by using Poisson distribution as above described. Oncogenic transformation of cells, which is a necessary intermediate step in the sequence of events leading to carcinogenesis, may presently be the most relevant cellular effect for simulating carcinogenesis.

Experimental studies indicate that after alpha particles hits, some of DNA cells are broken and biological effect originate[6,18]. If the cell is transformants, its cell cycle is changed shorter and mitosis rate is increased thus metabolism rate is increment and required more nutrient to continue life. Oncogenic transformation is predicted by sugarscape cellular automata model and compared with experimental data of mouse C3H 10T1/2 Cells exposure to alpha particles[19,20]. The result shows the number of transformant cells and oncogenic transformation are as a function of dose and has a liner relationship[19,20]. Variation of oncogenic transformation with dose is plotted in figure 2 and compared with Miller experimental data. The points are the results of several independent run, performed in different time. The sugarscape cellular automata model has predicted transformation frequency/ surviving cells, number of initial infected, number of transformants cells and lung cancer risk which are listed in table 1.

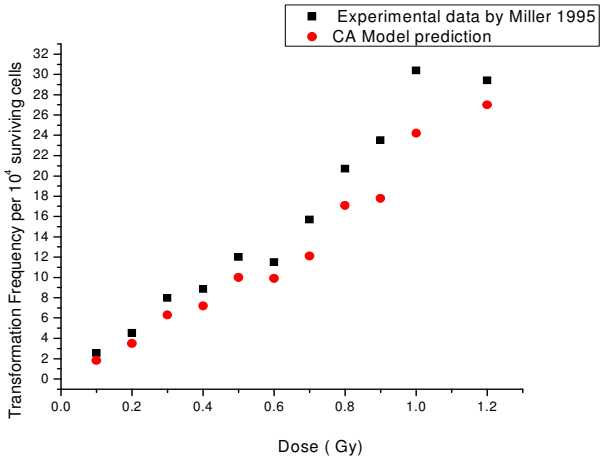

Figure-2
Trasformants per surviving cells for exposure of Radon progeny alpha particles predicted by CA model and comparison with experimental data of C3H 10T1/2 cells exposure to alpha particles[16]

Lung cancer risk is obtained by dividing the obtained infected cells by alpha particles traversals per initial normal cell. Comparison of sugarscape cellular automata prediction with epidemiological, dosimetric and biological lung cancer risk data is plotted in figure 3. The comparison of lung cancer risk prediction of CA model with the epidemiological, dosimetric and biological data which displayed in figure-3, indicates the fair agreement between the results of the different approaches and the simulation results in the whole exposure range[7,21,22]. Figure- 4 shows that how the number of initial infected cells change during different metabolism landscape in sugarscape cellular automata model for Dose= 4 Gy. We consider thses states for changing cell from healthy to transformant based on cellular alpha particle hit and nutrient distribution.

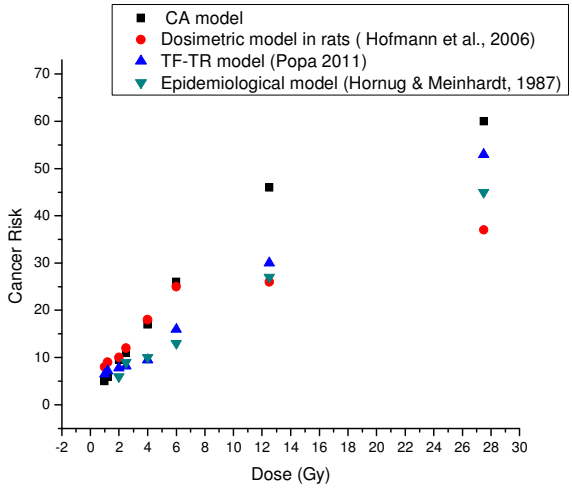

Figure-3
Epidemiological risk, risk of the TF-TR model (biological model) and risk data based dosimetric model in rats compared to the risk predicted with Sugarscape Cellular Automata model for 4 years exposure and different doses[7, 17, 18]

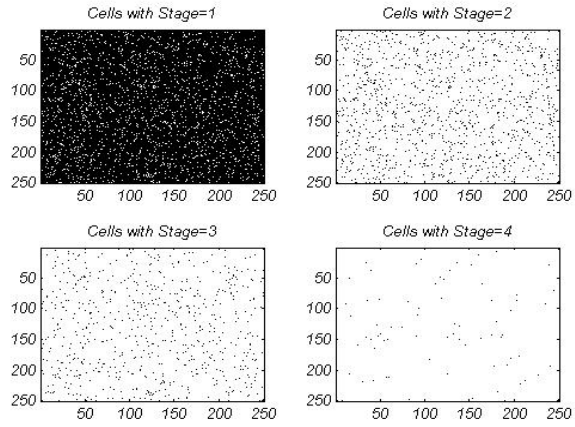

Figure-4
The number of lung cells in different stages of model based on Poisson distribution of alpha particle hit and Gaussian sugar distribution in each state. The number of cells are changed between these staged based on their metabolism rates. The cells in state 4 have the maximum metabolism rate and the most positional to become cancerous cell

Table-1
Transformation Frequency/ surviving cells, Number of initial infected, Number of Transformants cells and Cancer risk with around 39000 initial normal cells, predicted by CA model in different dose.

Dose	Initial normal cells	Infected cell predicted by Poisson distribution	Number of Transformant cells	Transformation Frequency/ surviving cells $\times 10^4$	Risk
0.1	39477	207	7	1.7732	0.5
0.2	39458	371	13	3.2946	1
0.3	39381	595	18	4.5707	1.5
0.4	39593	763	19	4.7988	2
0.5	39413	946	30	7.6117	2.4
0.6	39519	1118	39	9.8687	3
0.7	39435	1403	47	11.918	3.6
0.8	39451	1571	49	12.42	4
0.9	39432	1748	56	14.202	4.5
1	39579	1857	60	15.16	5
1.2	39400	2312	60	15.228	6
2	39518	37792	110	27.835	12
2.5	39398	4654	142	36.042	15
4	39584	6968	202	51.031	21
6	39676	10231	280	70.572	30
12.5	39488	18220	546	130.827	46
27.5	39588	29544	814	205.62	70

Conclusion

The purpose of this study is the assessment of lung cancer risk from Radon progeny alpha particles with using sugarscape cellular automata method. The lung cancer risk has predicted by focusing on information of hit probability and increasing metabolism rate of damaged cells. Metabolism as an important biomarker used in this model to follow states of damaged cells induced alpha particles hits to be oncogenic transformation states. The model also could cover all ranges of exposure time and doses. In the model, the importance of cell communication and metabolism has been identified as effective factors to tumor developing process.

The results indicated that lung cancer risk is proportional to the oncogenic transformation frequency and a function of average number of cellular alpha particle hits. Sensitivity and specificity of this model is compared favorably with previous lung cancer risk models such as epidemiological, dosimetric and biological (TF-TR) approaches. By comparison with other pervious methods, is concluded that the Sugarscape Cellular automata model predicts lung cancer risk with the highest precision, lowest error, simplest rule of the reality of the biological system, lowest time and the best fitness of complexity and stochastically of this phenomenon.

References

1. NRC, National Research Council, Health Effects of Exposure to Radon: BEIR VI, Washington D.C., National Academy Press, **(1999)**

2. ICRP 2010, The International Commission on Radiological Protection. Lung Cancer Risk from Radon and Progeny and Statement on Radon. ICRP 115, Elsevier Publisher **(2010)**

3. UNSCEAR 2000, Sources and Effects of Ionizing Radiation United Nations Scientific Committee of Ionizing Radiation United Nations, New York, Report to General Assembly, with Scientific Annexes, New York **(2000)**

4. EPA 1992, Environmental Protection Agency, Technical support document for the 1992 citizen's guide to Radon **(1992)**

5. ICRP 1991, The International Commission on Radiological Protection. ICRP Publication 60, Ann. ICRP 21 (1-3) **(1991)**

6. Hofmann W., Truţă-Popa L.A. and Fakir H., Mechanistic Model of Radon-Induced Lung Cancer Risk at Low Exposure. Proceedings of the IRPA Conference, Paris; Available at: http://www.colloquium.fr/06IRPA/CDROM /docs/P-017.pdf **(2006)**

7. Truta Popa L., Models for the assessment of lung cancer risk, PhD thesis, Babes – Bolyai University, 146 pp **(2010)**

8. Truta-Popa L.A., Hofmann W. and Cosma C., Prediction of Lung Cancer Risk for Radon Exposure Based on Cellular Alpha Particle Hits, *Radiat. Prot. Dosim*., 1–6, **(2011)**

9. Fleishman L., Crawford-Brown D. and Hofmann W., A computational model for radiation-induced cellular

transformation to in vitro irradiation of cells by acute doses of X-rays, *Math. Biosci.,* **215**, 186–192 **(2008)**

10. Wolfram S., A New Kind of Science, Wolfram Media publisher **(2002)**

11. Bar-Yam Y., Dynamics of complex systems. New England Complex Systems Institute **(1997)**

12. Rahman A., Setayeshi S. and Shamsaei M., Wealth adjustment using a synergy between communication, cooperation, and one-fifth of wealth variables in an artificial society, *AI & Soc.,* 24:151–164 **(2009)**

13. Nourafza N., Setayeshi S. and Khadem-Zadeh, A., Design a cellular sugarscape environment to increase the learning speed in a stochastic multi-agent network, *Inter. J. Info. Commun. Tech.,* **3(4)**, 65-72 **(2011)**

14. Nourafza N., Setayeshi S. and Khadem-Zadeh A., A novel approach to accelerate the convergence speed of a stochastic multi-agent system using recurrent neural nets, Neural, *Comput & Appl.,* **21(8)**, 2015-2021 **(2012)**

15. Epstein J.M. and Axtell R., Growing artificial societies: social science from the bottom up. Brookings Institution Press, Washington DC, **(1996)**

16. Buzzing P.C., VUSCAPE: communication and cooperation in evolving artificial societies, Master's Thesis, Artificial Intelligence Department of Computer Science, Faculty of Sciences, Vrije University, Amsterdam **(2003)**.

17. Bhatt A. N., Mathur R., Farooque A., Verma A. and Dwarakanath B. S., Cancer biomarkers - Current perspectives, *Indian. J. Med. Res.,* **132**, 129-149 **(2010)**

18. Hofmann W., Fakir H., Aubineau-Laniece I. and Pihet P., Interaction of Alpha Particles at the Cellular Level-Implication for the Radiation Weighting Factor, *Radiat. Prot. Dosim.,* **112**, 493–500 **(2004)**

19. Miller R.C., Marino S.A., Brenner D.J., Martin S.G., Richards M., Randers-Pehrson G. and Hall E.J., The biological Effectiveness of Radon – Progeny Alpha Particles. II. Oncogenic Transformation as a function of Linear Energy Transfer, *Radiat. Res.,* **142**, 54-60 **(1995)**

20. Bettega D., Calzolari P., NorisnChiorda G. and Tallone-Lombardi L., Transformation of C3H 10T1/2 Cells with 4.3 MeV alpha particles at Low Doses: Effect of Single and Fractionated Doses, *Radiat. Res.,* **131**, 66-7 **(1992)**

21. Hornung R. and Meinhardt T., Quantitative risk assessment of lung cancer in U.S. uranium miners, *Health Phys.,* **52**, 417-430 **(1987)**

22. Hofmann W., Crawford-Brown D. J., Fakir H. and Monchaux G. Modeling lung cancer incidence in rats following exposure to Radon progeny, *Radiat. Prot. Dosim.,* **122**, 345–348 **(2006)**