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## INTEGRATION OF COMPUTATION METHODS INTO RADIATION STERILIZATION PROCESS

**V.T. Lazurik, V.M. Lazurik, G.F. Popov, Yu.V. Rogov, Z. Zimek\***

*V.N. Karasin Kharkiv National University, 4 Svobody Sq., 61077, Kharkiv, Ukraine*

*\*Institute of Nuclear Chemistry and Technology, Ul. Dorodna 16, 03-195, Warsaw, Poland*

*E-mail: popov@univer.kharkov.ua*

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Authors have developed the computer technology for simulation of practical tasks in radiation sterilization process in accordance with Method 1, Standard ISO 11137 and IAEA Code of Practice. The technology was realized on the base of the RT-Office modules for modeling by Monte Carlo method of an absorbed dose in an irradiated heterogeneous targets with electron beam (EB), X-ray and gamma-ray and specialized software ModeSAL. The software ModeSAL was used for simulation and comparative analysis of a sterility assurance level (SAL) and a sterilizing dose for bioburden to achieve a required SAL in an irradiated product. The mathematical approach of the technology is based on the detailed and precise consideration of a self-consistent physical and geometrical models of calculation an EB, X-ray and gamma-ray dose maps in an irradiated product, a SAL, a sterilizing dose and the spatial and time uncertainties for dose provided to an irradiated product. The analysis of interrelations between parameters of EB radiation facility and values of a SAL and a sterilizing dose are considered.

**KEY WORDS:** radiation sterilization, Standard ISO 11137, RT-Office, software ModeSAL, dose map

Radiation sterilization process of health care products is well established technology and becomes one of the continuously growing branches of radiation processing. Quality Assurance and Quality Control (QA&QC) for all procedures of radiation sterilization is regulated by standards ISO 11137, ISO 13485 [1,2]. For determination of the sterilization dose for required sterility assurance level (SAL) of microbial population on/in an irradiated product, the mathematical model and methods simulation 1 and 2 were developed and experimentally verified [1,3,4,5]. The methods are based on a probability model for the inactivation of microbial population.

The features of mathematical model which is used in the Method 1 are the following [4,5]:

- the probability of microbial survival within the population diminishes exponentially with increasing radiation treatment of product by EB, X-ray or gamma-ray;
- the inactivation of any one type of microorganism contributing to the bioburden of the product units can be described by its own unique  $D_{10}$  value, where  $D_{10}$  is characterize the radiation resistance of microbes.  $D_{10}$  is the radiation dose that will reduce a microbial population by 90%;
- the probability of survival of population from  $N$  microbes (bioburden) at irradiation is determined by binomial law;
- the number of microbes on/in product unit is defined by Poisson distribution.

In this model, it is suggested that dose value in all product volume during time of irradiation is constant. The constant is chosen as minimum value of an absorbed dose ( $D_{min}$ ) in the dose map of an irradiated product.  $D_{min}$  is called as a sterilization dose. The value of sterilization dose ( $D_{min}$ ) required to achieve a given SAL for average bioburden of microbial population with standard distribution of resistances (SDR) are presented in the Tables form in the ISO 11137 and IAEA Code [1,3].

The mathematical model for calculation a sterilization dose do not take into consideration the spatial non-uniformity of absorbed dose in an irradiated materials and the uncertainties of irradiation process on results sterilization. It is well known, that under irradiation with EB, X-ray or gamma-ray of heterogeneous targets near the boundaries of contacting materials with different density and/or atomic number an appearance of anomalies in a dose map is observed [6,7]. Under products sterilization, the characteristics of radiation facility can be fluctuated and changed during time irradiation. These effects can be essential influence on the probability of microbial survival and on a sterilizing dose value. Authors developed the computer methodology for simulation of practical tasks in radiation sterilization process based on the detailed and precise consideration of a self-consistent physical and geometrical models for simulation EB, X-ray and gamma-ray dose maps in irradiated product, the uncertainties of irradiation process, a SAL and a sterilizing dose [8].

The objective of this study was the detailed computer analysis of influence of the space non-uniformity of EB absorbed dose distribution in irradiated products and the uncertainties of irradiation process on characteristics of EB sterilization process.

### COMPUTATION APPROACH TO DECISION OF PRACTICAL TASKS IN RADIATION STERILIZATION PROCESS

Authors have developed the information system for analysis and optimization of problem tasks of the radiation sterilization process on the base of specialized simulation modules of Radiation Technological Office (RT-Office) [6].

The system includes the RT-Office modules for simulation of an absorbed dose in irradiated targets with EB, X-ray and gamma-ray and specialized software ModeSAL [8]. The software ModeSAL is intended for simulation and comparative analysis of a SAL and a sterilizing dose for bioburden in an irradiated product. The ModeSAL code is a scientific tool which is accessible for broad audience of users, such as microbiologists, dosimetrists, physicists, and other specialists working with radiation sterilization tasks.

Some practical tasks which can be decided with help of the ModeSAL code are as follows:

1. Software ModeSAL allows calculate the sterilized dose required to achieve a given SAL for an arbitrary values of average bioburden having SDR on the base of  $D_{min}$  accordingly Method 1 ISO 11137 and IAEA Code.

It means that:

- ♦ for all values average bioburden from the Tables of ISO 11137 and IAEA Code having SDR, the data calculated by ModeSAL and the Tables data are in an absolute agreement;
  - ♦ for an arbitrary values of average bioburden having SDR and which are absent in the Table, the Software ModeSAL calculates exactly the value of sterilized dose required to achieve a given SAL. I.e. in this case, user can use these data without interpolation of the Table 5 data.
2. Software ModeSAL allows calculate the sterilized dose required to achieve a given SAL for an arbitrary values of average bioburden having any distribution of resistances on the base of  $D_{min}$  accordingly Method 1 ISO 11137 and IAEA Code.

It is useful in case, when user works with known dangerous viruses or known microbial populations which are differed from SDR, for example, in case of bioterrorism (anthrax, bird's influenza, etc.). User can take the value of microbial resistances for dangerous viruses, for example from "Database on Microbial Resistance to Radiation", and enter as input data to the Software ModeSAL [10]. With help of the Software ModeSAL user can made PC experiment to estimate the necessary absorbed dose and radiation facility parameters to eliminate the known dangerous viruses or known microbial populations.

3. Software ModeSAL allows calculate the sterilized dose required to achieve a given SAL for an arbitrary values of average bioburden having any distribution of resistances on the base of  $D_{min}$  accordingly Method 1 ISO 11137 and IAEA Code with due regard for:
  - ♦ an uncertainty effect of absorbed dose and of parameters of process irradiation;
  - ♦ an uncertainty effect in a composition and in radiation resistances of microbial population.
4. Software ModeSAL allows calculate the sterilized dose required to achieve a given SAL for above points 1, 2, and 3 with regard to the dose distribution in an irradiated product.

Comparison of calculation results on the base of  $D_{min}$  accordingly Method 1 ISO 11137 and IAEA Code with regard to the dose distribution in an irradiated product allows to estimate the "safety factors" for mathematical models which are used in the Standard ISO 11137 and in the Software ModeSAL.

Analysis and solution of problem tasks in radiation sterilization technology were performed as follows:

- ♦ The RT-Office modules for specific EB, X-ray and gamma-ray radiation facility and irradiated products optimize a thickness of irradiated products, a configuration of package for the product, the method of irradiation as one- or two-sided types, the choice of irradiation regimes.
- ♦ The RT-Office modules simulate a profile of an absorbed dose map in an irradiated product for optimal irradiation regimes.
- ♦ Simulation prediction for the dose map should be periodically verified in special dosimetric experiments.
- ♦ The output results for EB, X-ray and gamma-ray processing simulated with the RT-Office modules for an absorbed dose in forms of probability distribution and space distribution (dose map) are used directly as input data for the software ModeSAL;
- ♦ The software ModeSAL determines the sterilization dose and scale factor for parameters of radiation facility to achieve a required SAL for microbial population on/in an irradiated product in accordance with Method 1 ISO 11137 or IAEA Code. The software ModeSAL decides as well known and established tasks, so the specific practical tasks in radiation sterilization technology.
- ♦ The RT-Office modules optimize the operational parameters of radiation facility on the base of scale factor data.

Such execution sequence of work provides a computer technology for sterilization process in accordance with Method 1 ISO 11137 and IAEA Code with regard to the spatial and time uncertainties for dose delivery to irradiated product.

### EB DOSE MAPPING IN HETEROGENEOUS TARGET

As example, for decision of some practical tasks in sterilization technology, the EB sterilized process was analyzed with the use software ModeStEB for simulation of EB absorbed dose in heterogeneous targets [9, 11]. The software ModeStEB was specially designed for simulation by a Monte Carlo method in 3D model of the absorbed dose and charge distributions within multilayer packages irradiated with scanned EB on industrial radiation facility that is based on the pulsed or continuous type of electron accelerators in the electron energy range from 0.1 to 25 MeV. The self-consistent physical and geometrical models of the program ModeStEB include in detail the features of electron

beam transport and dose field formation in the multi-layer targets. The feature of the software ModeStEB is unique high running speed of calculation schemes. It is reached due to use of specially developed algorithm on the basis of a method of translation of an electron trajectory and an optimum choice of free parameters of modeling.

Multi-layer target consists of some identical packages with flat sheets of materials with various density and atomic number. The number of packages are in the range from 1 to 10. The number of layers in the each package with various geometrical sizes are in the range from 1 to 6. Multi-layer target with/without packing box can be located on the conveyer platform horizontal, vertical or under arbitrary angle relatively incident EB axis.

The software ModeStEB use as input data a detailed characteristics of radiation facility and irradiated target including:

*Parameters of electron beam* - average beam current, or pulse duration and repetition rate in pulsed accelerators, electron energy spectrum, beam diameter and spatial distribution of the beam intensity.

*Parameters of scanned system* - modes of operation - the triangular or non-diverging irradiation treatment field in target material; height of scan horn and width of scanning; distance scan - conveyer; form of current in magnet of scanned system; repetition frequency of scanning.

*Parameters of conveyer line* - speed and geometrical characteristics.

*Parameters of irradiated product* - geometrical characteristics of the irradiated product; elemental composition of the target; material and size of the covering for irradiated product.

The software ModeStEB provides users with data set in the graphic and tabular form for dose map and charge deposition within each layer of the multi-layer target irradiated with a scanned EB. The output results for EB absorbed dose in an irradiated target are represented in forms of probability distribution and space distribution (dose map). The results for EB absorbed dose in multi-layer target were directly used as input data for the software ModeSAL for further analysis of radiation sterilization process.

#### **THE FEATURES OF STERILIZATION PROCESS UNDER SPATIALLY NON-UNIFORM DOSE DISTRIBUTION**

The results of EB absorbed dose in an irradiated target simulated with the software ModeStEB are used as input data for the software ModeSAL. The features of mathematical model of the software ModeSAL are the following:

- The generalized stochastic model of radiation sterilization process is developed.
- The basic stochastic parameters proper in the modern radiation technologies are taken into account.
- To such stochastic parameters refer to: the bioburden in a product and in its separate parts; a spatial distribution of microbes in a product; a spatial dose distribution in an irradiated product; uncertainties because of nonstability of radiation facility parameters in time of irradiation; operational characteristics of radiation facility required to achieve a given SAL.

The feature of the theoretical approach at development of the generalized stochastic model of radiation sterilization process is introduction of the scale factor (SF). SF is the basic characteristic of change of an irradiation process for the analysis of uncertainties effect. It is well-known, that the dose map depends on major number of parameters of an irradiation process. For example, beam current, energy of ionizing particles, width of scanning, conveyer speed, as well as the characteristics of irradiated product are related to the basic operational parameters which are influenced on the dose map.

However, if we are interested the uncertainties related only with irradiation system, it is logical to assume, that profile of an absorbed dose distribution will change much less than a dose value in separate points. I.e. small changes of irradiation facility parameters basically results in proportional (scale) change of a dose value in all points of the dose map. This fact is obvious for basic operational irradiation parameters, such as a beam current and a conveyer speed. Less obviously, however, with good precision it refers to both to scanning width and to distance from exit window of accelerator to irradiated object. Concerning changes of a dose map at change of energy of ionizing particles, this supposition generally is not valid.

Thus the radiation interaction with a product in the stochastic model is described by some dose map, for which all changes are considered as proportional to a SF value. Consequently, stochastic uncertainty is easily reduced to uncertainty of SF value. The statistical distribution of a SF is supposed as a normal distribution. Therefore, a value of one standard deviation of SF is selected as characteristic of statistical uncertainty for specific radiation processing.

The computer technology represents a simulation results in a graphical and tabular forms. That provides cognitive and comparative analysis of influence of uncertainty values of radiation processing and bioburden characteristics on a SAL of irradiated product.

Fig.1 represent the form of the software ModeSAL with loaded input data of EB absorbed dose for calculation of SAL and sterilized dose. The absorbed dose in an EB irradiated target was simulated by software ModeStEB. The absorbed dose is represented in form of probability distribution (graphs and Table) and space distribution (see Fig.1, left side).

There is a possibility to calculate, analyze and compare results for microbial population with SDR taken from ISO 11137-2, 2006 and IAEA Code, for distributions of resistances MD1-MD20 taken from the paper, as well as on the base of any microbial population for which a distribution of resistances can be enter as input data by manually (see Fig.1,

Table, right side) [5].

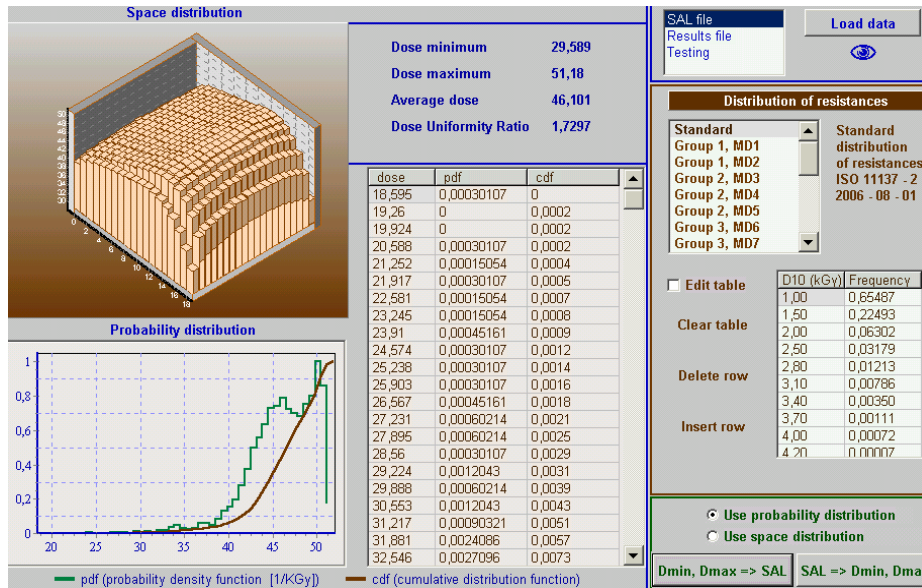


Fig.1. The forms with input data on absorbed dose in PE block under one-sided irradiation with scanned 10 MeV electron beam on moving conveyer. 3D view - dose map, 2D view and Table data – probability distribution of absorbed dose.

The results of SF,  $D_{max}$  and  $D_{min}$  calculation as function of average bioburden (Av.B) for microbial population with distributions of resistances MD15 are presented in Fig.2. Microbial population is located on/in PE block under two-sided irradiation with 10MeV electron beam. Calculations were made on the base of EB dose map presented in Fig.1. for Av.B = 1000, SAL= $10^{-6}$  and uncertainties  $\pm 5\%$  the SF = 0.4956. It is necessary to change the operational parameters of EB radiation facility (EB current, conveyer speed,...) on SF = 0.4956 value to achieve a required SAL= $10^{-6}$ .

The calculations results for comparative analysis of a SAL and a sterilizing dose for microbial population with distributions of resistances both as SDR and MD15 types for Av.B = 1000 in two-sided irradiated product with 10MeV EB are presented in Fig.3. Calculations were made for non-uniform dose distribution of EB presented in Fig.1. As it is seen from Fig.3, for microbial population MD15 at calculated SF = 0.4956 and uncertainties  $\pm 5\%$ , the SAL= $10^{-6}$  for Av.B = 1000.

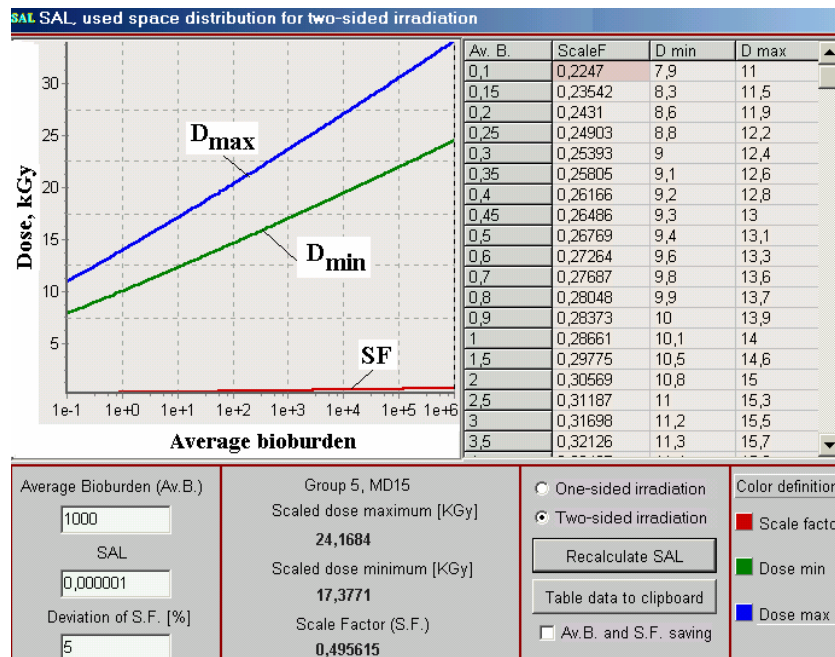


Fig.2. The values of  $D_{max}$ ,  $D_{min}$  and SF as function of average bioburden for microbial population MD15 in graphical and tubular forms. PE block is two-sided irradiated with 10 MeV electron beam.

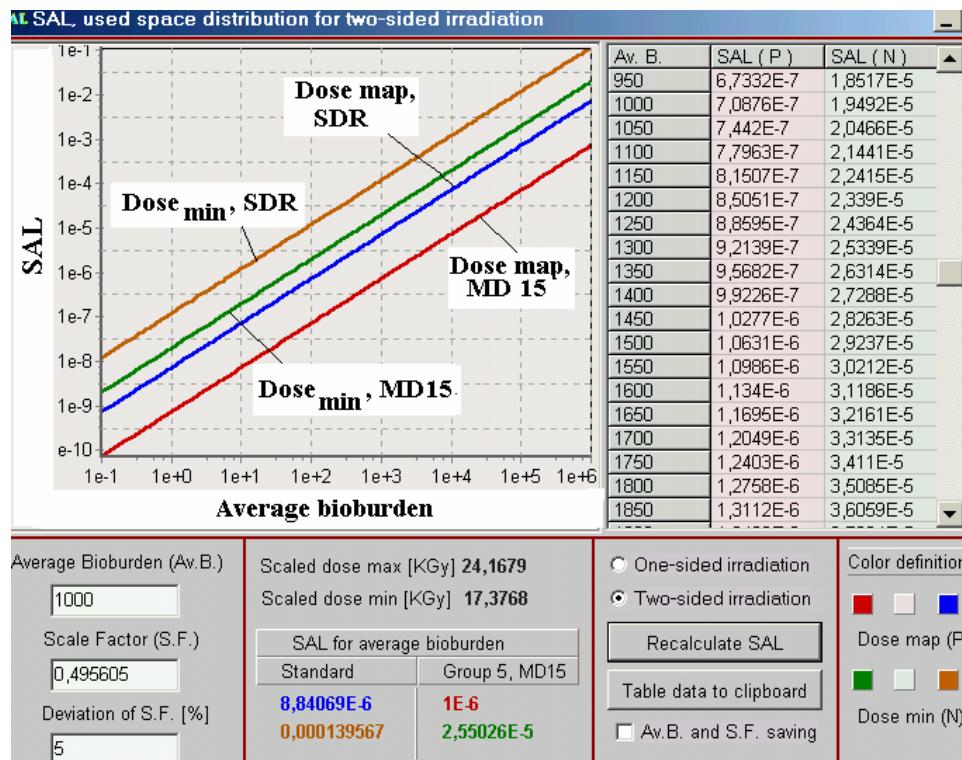


Fig.3. The values of SAL as function of average bioburden for microbial populations SDR in graphical form and MD15 in graphical and tubular forms. PE block is two-sided irradiated with 10 MeV EB, Av.B = 1000, SF = 0.4956, and uncertainties  $\pm 5\%$ .

The results of comparative analysis of values of SF and EB sterilized dose for microbial populations with distributions of resistances both as SDR and MD15 types calculated on the base of  $D_{\min}$  and dose map PE block under two-sided irradiation with 10MeV with 10MeV EB are presented in the Table.

Table. The results of comparative analysis of values of SF and EB sterilized dose for microbial populations SDR and MD15 calculated on the base of  $D_{\min}$  and dose map.

Microbial population	Unc,%	Dose map (P), kGy			Dose min (N), kGy		
		SF	$SD_{\min}$	$SD_{\max}$	SF	$SD_{\min}$	$SD_{\max}$
SDR	0	0,5715	20,04	27,87	0,709	24,86	34,57
	10	0,6218	21,8	30,32	0,775	27,18	37,8
MD15	0	0,4852	17,01	23,66	0,5968	20,9	29,1
	10	0,5332	18,7	26,0	0,6601	23,14	32,19

The analysis of results represented in Fig.3 and the Table data shows, that for microbial populations of SDR and MD15 types in all range of average bioburden the SAL value calculated on the base of suggestion, that  $D_{\min}$  is constant in all irradiated product volume, is greater than the SAL calculated on the base of a spatial EB dose distribution in the irradiated product. It follows from these results that value of EB sterilizing dose in case of calculation on the base of  $D_{\min}$  is greater in comparison with calculation of sterilizing dose on the base of dose map in an irradiated product. Taking into account the uncertainties due to fluctuation of irradiation parameters leads to increasing of sterilizing dose value. Irradiation regime on the base of  $D_{\min}$  concept leads to overdosing of the sterilized product. And as result, it can reduce the throughput and worsen quality of the products.

### CONCLUSION

The information system for analysis and optimization of problem tasks for radiation sterilization process on the base of specialized simulation modules of Radiation Technological Office was developed. The mathematical approach of the information system is based on the detailed and precise consideration of a self-consistent physical and geometrical models of calculation an EB, X-ray and gamma-ray dose maps in irradiated product, the uncertainties of irradiation process, a SAL and a sterilizing dose.

The integration of the developed computational technology in Standard ISO11137 and IAEA Code expands possibility and enhances quality assurance and quality control of the use of the Standards for decision of problem tasks

in radiation sterilization process. It is established due to appearance of new opportunities, such as: more precise determination a sterility assurance level and a sterilizing dose with taking into consideration a spatial and time heterogeneity for dose distribution in irradiated product; possibility to optimize irradiation modes of sterilized product to achieve a required SAL for microbial population on/in an irradiated product; possibility to work with any composition of microbial populations.

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#### ИНТЕГРИРОВАНИЕ ВЫЧИСЛИТЕЛЬНЫХ МЕТОДОВ В ТЕХНОЛОГИЮ РАДИАЦИОННОЙ СТЕРИЛИЗАЦИИ

**В.Т. Лазурик, В.М. Лазурик, Г.Ф. Попов, Ю.В. Рогов, З. Зимек\***

*Харьковский национальный университет им В.Н. Каразина, пл.Свободы 4, 61077 Харьков, Украина*

*\*Институт Ядерной Химии и Технологий, ул. Дородна 16, 03-195, Варшава, Польша.*

Разработана компьютерная технология для решения практических задач процесса радиационной стерилизации в соответствии со стандартом ISO 11137 и кодами практики МАГАТЭ. Технология реализована на основе модулей RT-Office и специализированного программного обеспечения ModeSAL. Модули RT-Office предназначены для расчета методом Монте-Карло поглощенной дозы в гетерогенных мишенях, облучаемых пучками электронов, тормозным или гамма излучением. Программное обеспечение ModeSAL использовалось для моделирования и сравнительного анализа уровня стерильности и стерилизационной дозы для микробной контаминации в облучаемом продукте. Математический подход технологии основан на детальном и корректном учете самосогласованных физических и геометрических моделей расчета поля дозы электронов, тормозного и гамма излучения, уровня стерильности и стерилизационной дозы а также пространственных и временных неоднородностей дозы в облучаемой мишени. Проводится анализ взаимосвязи между параметрами радиационного оборудования пучков электронов и величинами уровня стерильности и стерилизационной дозы.

**КЛЮЧЕВЫЕ СЛОВА:** радиационная стерилизация, стандарт ISO 11137, RT-Office, программа ModeSAL, карта дозы