

BRIEF  
COMMUNICATIONS

# Study of Biological Effects by Pulsed Bremsstrahlung Radiation of Ultrahigh Dose Rate at the Angara-5-1 Facility<sup>1</sup>

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**Abstract**—Radiological methods of treatment of malignant tumors are widespread in medical practice. In addition to the type of radiation and dose and fractionation of the radiation regime, the dose rate is one of the factors that affects the effectiveness of treatment. The therapeutic dose rate lies in the range of tens of mGy/s. At modern high-current accelerators of relativistic electron beams, a significant increase in the dose rate to hundreds of MGy/s is achievable, which is more than 10<sup>8</sup> times greater than the therapeutic dose rate. It is difficult to predict the nature of processes in tissues and its cells at such radiation intensities. To determine the effect of extreme dose rate on the radiosensitivity of tissues at the Angara-5-1 facility, experiments were conducted to determine the lethal dose (LD50/30) for laboratory mice. Our result on the study of the LD50/30 dose (~100 MGy/s) allows us to make a conclusion about a possible higher lethal dose than the power range of the doses used for medical purposes.

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## 1. INTRODUCTION

Radiological methods of treatment of malignant tumors are widespread in medical practice. Specialized medical accelerators or radioisotope sources are used for photon or electron irradiation. In addition to the type of radiation and dose and fractionation of the radiation regime, the dose rate is one of the factors that affects the effectiveness of treatment. In typical situations, the therapeutic dose rate is tens of mGy/s. If we assume that the average photon energy of a medical accelerator with a power of up to 1 kW is about 1 MeV, then, in a cell with a characteristic size of 10 μm averagely absorbed 10 photons per second. Thus, the acts of the primary interaction of photons with the cell are separated by a time interval of 1–10 ms.

At the same time, due to the appearance of the degradation spectrum of secondary electrons, this time is reduced by several tens of times. On modern high-current accelerators of relativistic electron beams, as well as on pulsed laser installations, a significant increase in the dose rate to hundreds of MGy/s is achievable.

At the same time, the dose rate increases more than 10<sup>8</sup> times. Such a sharp change in the intensity of the radiation dose increases the density of free electrons and the resulting radicals in the cell, which can lead to qualitative changes in the reaction of the cell to radiation.

It is also possible to develop nonlinear effects in a cell with multiple, simultaneously formed DNA damages, and other mechanisms. The characteristic changes for normal and tumor cells at ultrahigh irradiation intensities may differ. In the literature, there are separate studies of DNA changes at comparable dose rates, but there is no information about the effect of ultrahigh dose rates on the therapeutic effects of irradiation of malignant tumors. Previously, we have shown [1, 2] that biological effects caused by radiation with ultrahigh dose rate have a number of specific features. Thus, in normal and tumor cells, the induction of apoptosis increases and the number of cells that die along the path of necrosis decreases. These and available literature data may indicate potential differences in the effects of irradiation of individual cell structures and tissues in vivo.

<sup>1</sup> The article was translated by the authors.

In assessing the effects of ionizing radiation on whole organisms, one of the fundamental indicators is the LD50/30 characteristic. This characteristic was especially actively studied in the 1950s–1960s at the dawn of the practical use of nuclear energy. Currently, more attention is paid to cellular and tissue effects, as well as molecular mechanisms of interaction of ionizing energy and biological objects. At the same time, LD50/30 remains a classical value for describing the characteristics of a particular type of radiation.

The aim of the present experimental study was to determine the effect of superintense bremsstrahlung X-rays on the radiosensitivity of laboratory mice by determining the dose LD50/30.

## 2. MATERIALS AND METHODS

The object of the study were 40 outbred laboratory mice irradiated once with superintense pulsed bremsstrahlung radiation with a pulse duration of 30–70 ns and a basic photon energy of 50–700 keV.

The experiments were carried out at the Angara-5-1 facility [3], which is a pulsed electric power generator consisting of eight modular generators connected in parallel. The stored energy of the facility is 1.2 MJ. Each module [4] generates an electromagnetic pulse of a megavolt range with a full width at half-maximum (FWHM) of 90 ns and transmits it to the load via a magnetically insulated transmission line (MITL).

To create a powerful X-ray source, the Angara-5-1 was switched into a beam mode. Due to specific features of electron beam formation in a diode with a current of 2–3 MA, it was decided to use separate eight diodes installed at the output of each module of the facility [5].

When a voltage pulse with an amplitude of up to 700 kV is applied to the diode, an accelerated electron beam is formed. During its deceleration at the anode, the electron beam generates a pulse of bremsstrahlung radiation with a boundary photon energy equal to the potential difference between the anode and the cathode.

The horizontal and vertical distributions of the doses were calculated.

In calculations, we used the waveform of the voltage at the diodes in one of the shots. The diode current was determined from the voltage by the 3/2-law at each time moment. The radiation power was taken proportional to the product of the current and the voltage. The spectral radiation density at each time was calculated by the Kramers formula.

The calculations took into account that the radiation passed from the diodes to each point at its own angles. Absorption in 7-mm-thick duralumin and in a water or air column was taken into account. The absorption length depends on these angles. It was assumed that the attenuation of radiation in the medium was described by Booger's law. The calcula-

tions were performed for air and water, as a medium closest in absorption to living tissues. The dependences of the mass attenuation coefficients on the photon energy were taken from [6].

As a result of calculations, it was found that the relative dose gradient of X-ray bremsstrahlung in the container was 6.5%/cm along the horizontal coordinate  $x$  and 14%/cm along the height.

It should be noted that these calculations are only estimates. The fact is that the physics of a high-current electronic diode is greatly complicated by the appearance of plasma on the surfaces of the electrodes. Plasma also occurs on the MITL surface. The presence of plasma on the surfaces of the electrodes leads to a change in the effective gap length between the cathode and the anode; as a result, the effective impedance changes and the 3/2-law fails to work. In addition, plasma expansion leads to an increase in leakage currents. The latter leads to a voltage drop on the diode and a change in the radiation spectrum, which is not taken into account in the calculations. Thus, the appearance of plasma on the electrodes greatly changes the physics of the high-current diode.

The mice were irradiated in a special metal cylinder (Fig. 1). The bottom of the cylinder was located at a distance of 15 mm from the tantalum foil, which served as a source of bremsstrahlung radiation. To filter the soft component of the radiation spectrum, the bottom of the cylinder was made of 7-mm-thick duralumin.

Each mouse was placed in a 35 × 35 × 80-mm cardboard container. Two sets of thermoluminescent dosimeters (TLDs) were attached to the top and bottom of the container (Fig. 2). The containers with dosimeters were placed in two layers, each layer having five containers. Thus, 10 mice were trained simultaneously.

Metrological assurance of dosimetric measurements was provided SAD1M diamond dosimeters and TLDs.

Three SAD1M diamond X-ray dosimeters [7] were used to record the dose rate at the bottom of a cylindrical metal box. The dosimeter provided recording of pulsed bremsstrahlung radiation with a maximum dose rate per pulse in the range from  $10^9$  to  $10^{11}$  R/s. The SAD1M diamond dosimeter has a unique radiation resistance: its sensitivity varies by no more than 5% after irradiation with electron or photon radiation dose of  $5 \times 10^5$  rad.

Since the size of the SAD1M diamond dosimeter is 12 mm, the positioning error of the dosimeter, which randomly varied from shot to shot, was a very significant factor.

Radiation-sensitive elements of TLDs are thermoluminescent detectors, which allow to detect doses in the range of 0.00005–10 Gy with an error of  $\pm 15\%$ .

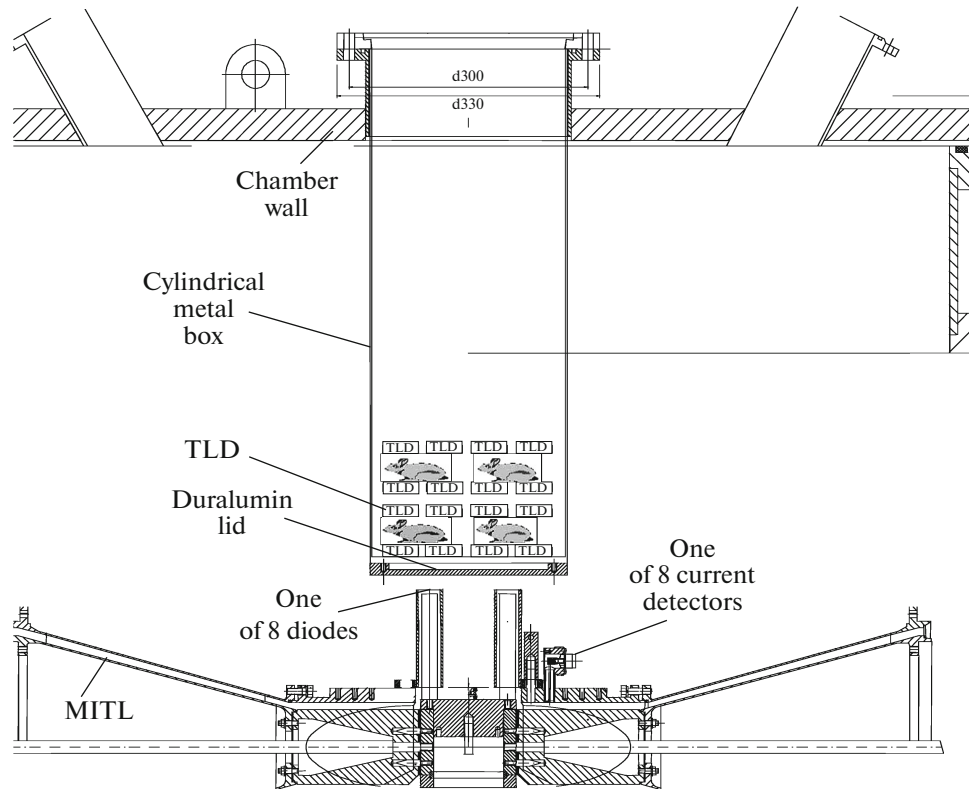


Fig. 1. Location of mice and TLDs on the Angara-5-1 facility.

TLDs were calibrated using a medical accelerator and showed a coefficient of variation of 2%.

### 3. RESULTS AND DISCUSSION

Four experimental shots were made. As a result, data from 12 diamond dosimeters and 160 TLDs were obtained.

Figure 3 presents an example of the recorded current, voltage, and dose rate signals. The amplitude of the dose rate was 0.3 GGy/s, and the FWHM duration was 38 ns. After integrating the dose rate signal, the dose rate of 10 Gy was obtained at the bottom of the metal cylindrical box.

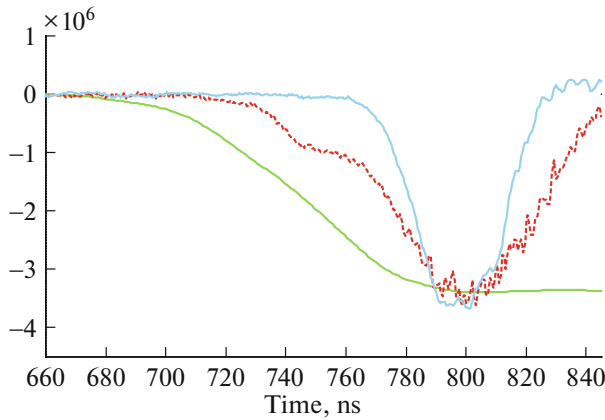
As was noted, the sets of TLD were attached to each container with a mouse on the top and bottom. Figure 4 shows the fixed doses arranged in ascending order: top of the container, bottom of the container, and their average value. This average value was taken as the dose received by the mouse.

The maximum dose fixed at the bottom of the container was 25 Gy. The maximum value of the average dose between the top and bottom was 17 Gy.

TLD recorded dose was smaller from the top than from the bottom. This is due to two more or less equivalent factors: for TLDs located on top, the distance to the emitter was greater, and, in addition, the absorption of radiation during the passage of cardboard and the body of mice was significant. From the fact that the absorption of radiation during the passage of cardboard and most mice was significant, it can be con-



Fig. 2. Upper row of containers with mice: 2A, 2B, 2C, and 2E. Upper container 2D is removed, and container 1D from the bottom row is seen instead of it. LTDs enveloped in paper are attached to each container. Three tubular supports for fixing diamond detectors are also seen.



**Fig. 3.** (Color online) Time profiles of the current and voltage of the Angara-5-1 facility and dose rate. The lower curve corresponds to the current pulse with an amplitude of 3.4 MA, the average curve corresponds to the voltage pulse with an amplitude of 700 kV, and the upper curve corresponds to the dose rate with an amplitude of 0.3 GGy/s.

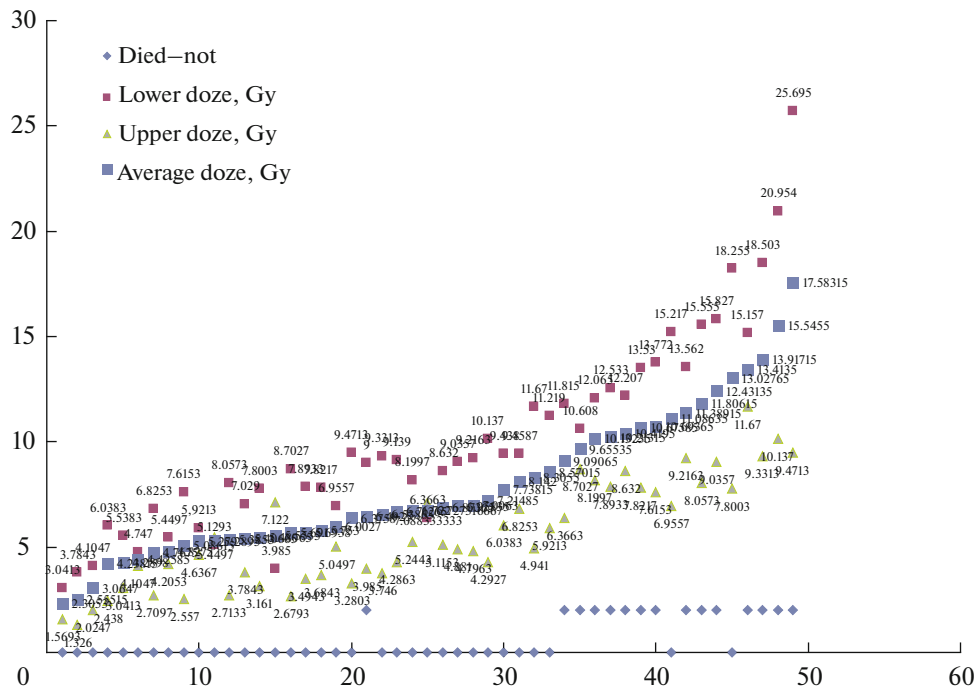
bremsstrahlung radiation with photon energy  $E$  is proportional to  $(E_0 - E)/E$ , where  $E_0$  is the energy corresponding to the diode voltage. Thus, the average photon energy will be about 200 keV, i.e., several times less than the energy corresponding to the applied voltage.

### 3.1. Study of Mice Survival Depending on the Dose Received

Classical experiments on the study of survival are carried out on groups of animals (or other organisms) stratified by the magnitude of the received dose. It was impossible to carry out such an experiment on the installation used. Therefore, we applied individual dosimetry and tried to estimate LD50/30 using both the classical probit analysis dividing the animals into groups with an equivalent dose as described below, as well as on the basis of the obtained survival data depending on the dose shown in Fig. 4.

cluded that the average photon energy was as low as 100–200 keV. Indeed, in Fig. 3, the maximum voltage amplitude was 700 kV. But this voltage is reached only at the maximum point, whereas during the entire pulse voltage, it is appreciably lower. In addition, it can be assumed that, at each time, the spectral density of

It is obvious that the problem of obtaining the exact value of the absorbed dose for each particular mouse with the available parameters of heterogeneity presents a significant difficulty. Probably, more accurate values could be obtained by conducting model experiments with the study of the absorbed dose distribution in tissues. However, we considered it possible to estimate this value using the average value obtained from four individual dosimeters for each animal. Assessing the results of animal death depending on the dose



**Fig. 4.** (Color online) Fixed individual doses for irradiated mice ordered in ascending order: from the top of the container (green triangles), from the bottom of the container (red squares), and their average values (blue squares). The dose (in Gy) is plotted on the ordinate, and the number of the mouse is plotted on the abscissa. Survival results for each mouse are also shown by blue diamonds with values 0 (live) or 1 (died).

received, it is noteworthy that, starting with an average dose of 8.8 Gy, almost all mice die. If, for example, take a sample of 14 mice with numbers from 27 to 40, it can be seen that, at a dose of 8.8 Gy, half of the mice in this sample died. Therefore, it can be assumed that the dose with 50% lethal outcome was 8.8 Gy in our experiments.

### 3.2. Probit Analysis of Mouse Survival Data after Total Irradiation at the Angara Facility

Four irradiation series, each with 10 mice, were performed. The individual dose for each mouse was determined as the arithmetic mean of the illumination results of four films (top: head and tail; bottom: head and tail).

Since there was a high inhomogeneity of the dose in both horizontal and vertical planes, the mice were placed in groups with a step of the dose range of 1 Gy (Table 1) and the percentage of mouse death in each group was determined, as well as probit analysis with the use of a standard statistical package (Statistics 6.0, StatSoft, USA) was conducted.

According to Table 1, the doses leading to the death of 99, 33, and 12.5% of the animals were 13.5, 9.5, and 5 Gy, respectively.

Figure 5 shows the results of LD50/30 calculation using probit analysis.

The value of LD50/30 determined by the method of probit analysis was 7.82 Gy, which is 1 Gy less than the qualitative assessment made on the basis of the analysis of the data of Fig. 4.

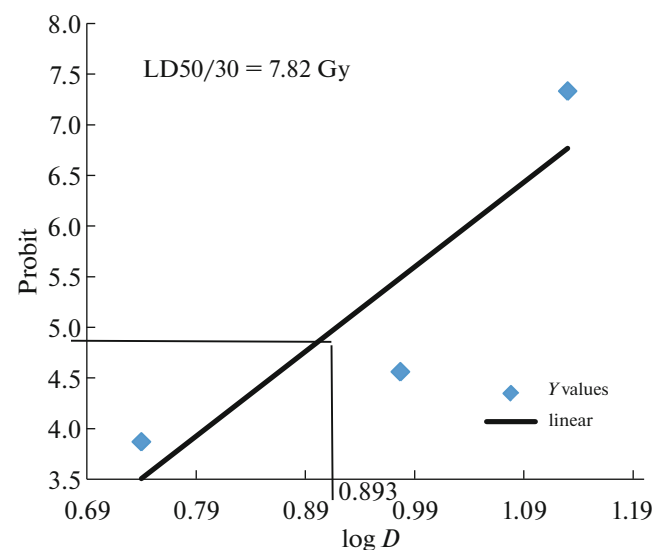
The value of LD50/30 for mice depend on many characteristics. It is shown that it depends on such genetic characteristics as, e.g., color [8]. White-coated mice tend to be more sensitive to ionizing radiation than black-haired mice. LD50/30 depends on the age and increases by about 1G for adult mice compared to young mice. For many years of research, it has been shown that LD50/30 depends on a set of characteristics of an organism and, first of all, on the characteristics of the main target for this indicator: bone marrow [9–11]. However, even its obvious properties, such as colony formation, do not always correlate with LD50/30 for a particular line of mice. If we summarize the basic data on the study of this indicator for mice, it ranges from 4 to 8 Gy according to different authors [8, 12, 13]. Thus, the detected value of DL50/30 lies at the upper limit of the range of values for mice irradiated with therapeutic photon beams of 0.3–1.2 MeV energy with a dose rate of 0.5–1.5 Gy/min [13]. It should be noted that most studies still indicate the upper limit of up to 7 Gy or less. The conditions of irradiation of mice on the used facility do not allow us to conduct a classical experiment to determine LD50/30, because, due to the large inhomogeneity of the bremsstrahlung beam, each mouse has an individ-

**Table 1.** Number of mice died for 30 days after exposure

Range of doses, Gy	Number of mice	Mice died
>15	1	1
14.1–15	3	3
13.1–14	4	4
12.1–13	–	–
11.1–12	1	1
10.1–11	–	–
9.1–10	3	1
8.1–9	–	–
7.1–8	1	0
6.1–7	3	0
5.1–6	8	1
4.1–5	5	1
3.1–4	6	0
<3	4	0
Total	39	12

ual dose significantly different from the neighboring mouse.

There is a strong vertical dose gradient that causes the dose received by the lower part of the animal to be two times higher than the dose received by the upper part of the animal. It is obvious that the integral dose under such irradiation conditions can be calculated by using Monte Carlo simulation. However, the graph of the dependence of the animal death on the average dose received by them (averaging of all four points of an individual dose measurement) clearly shows that, starting from the average dose of 8.8 Gy, almost all



**Fig. 5.** LD50/30 after irradiation of mice with an intense photon beam assessed by means of probit analysis.

mice die. The standard approach to the calculation of LD50/30 on the basis of probit analysis yields a value of 7.82 Gy; however, a qualitative assessment of the obtained results allows one to assume that this value can be 1 Gy higher. Probably, for a more adequate comparison of the effect of the dose rate on the animal death rates, it would be necessary to conduct a comparative irradiation of a group of animals with bremsstrahlung gamma radiation with a therapeutic dose rate having the same parameters of the dose distribution in space. However, the currently available radiation sources do not allow this to be realized.

#### 4. CONCLUSIONS

This study has shown that experiments on determining the biological effects of ultra-high-power gamma radiation have a number of methodological difficulties. First of all, they are related to the heterogeneity of the dose distribution, which requires either direct or model experiments (by using the Monte Carlo method) to calculate the dose to the entire body of the experimental animal and determine the absorbed dose attributable to the critical organs. The second important methodological problem is the lack of proven (and, in the future, necessary for medical use) methods of dosimetry. There are no experimental works evaluating the permissible range of the dose rates for different methods of dosimetry and evaluating errors and deviations, depending on the dose rate in the range of  $10^6$  Gy/s and above. However, the result obtained in our study of LD50/30 for a dose rate of  $\sim 100$  MGy/s allows us to conclude that LD50/30 for the studied line of mice is possibly higher than the range of dose rates used for medical purposes, which may indicate a higher radioresistance of normal tissues to such radiation [8, 12].

#### ACKNOWLEDGMENTS

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