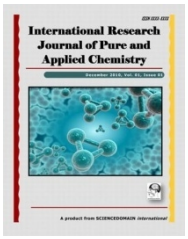

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Comparison of Biophysical and Radiological Responses of Bio-Test Objects to Pulsed and Continuous X-Ray and Neutron Irradiations

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Authors' contributions

This work was carried out in collaboration between all authors. All authors equally designed the study, performed the statistical analysis, wrote the protocol, and wrote different parts of the first draft of the manuscript. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: To correlate qualitatively and quantitatively biological effectiveness of irradiations of bio-test objects by neutrons, X- and gamma-rays within a wide range of doses, dose rates (dose powers), durations of action and spectral contents of the radiations.
Study Design: These irradiations were done with the help of well-known and newly elaborated sources of the above radiations based on isotopes, fission reactors, X-ray tubes and Dense Plasma Focus (DPF) devices.
Place and Duration of Study: Institute of Metallurgy and Material Science (IMET), Institute of Plasma Physics and Laser Microfusion (IPPLM), Moscow State University (MSU), and Medical Radiological Research Center (MRRC), between June 2007 and December 2011.

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Methodology: As biological test objects of different contents and complexity we used enzymes of various types, serum, seminal fluid, human lymphocytes. Enzymes activity prior to and after irradiation was measured using spectrophotometer (Hitachi) within the wavelength range $\Delta\lambda$ = 300÷750 nm according to up-to-date techniques. In the comparative researches the cytogenetic action of fission neutrons (generated by nuclear reactors) and of fusion 14-MeV neutrons (from DPF) were studied with the most widespread test-system – chromosomal aberrations in human lymphocytes.
Results: The range of the variations of the coefficient of biological effectiveness for neutron radiation of dissimilar dose rates (dose powers) and neutron spectra as a rule does not go out from the limits of physiological oscillations at the neutron dose power that changes within 9 orders of magnitude (till the figure 10^8 Gy/min) and it coincides with the "classic" dose rate effect (a quadratic part of dose curves for cell survival or chromosomal aberrations). Yet in the field of radioenzymology the very powerful X-ray radiation results in activation or suppression of enzymes at doses differing by 4-5 orders of magnitude (to lesser doses) compared with analogous effects obtained with low power isotope and X-ray tube sources.
Conclusion: Resemblance of neutron action on dose powers within 9 orders of magnitude gives hope of applicability of the DPF neutron generators for the potential methods of neutron therapy instead of dangerous, expensive and cumbersome nuclear reactors. But the anomalously strong X-ray influence upon enzymes dictates careful application of super-high power X-ray pulses and demands further investigations of the nature of these effects.

Keywords: Pulsed and continuous neutron and X-ray radiations; biological effectiveness; radioenzymology; chromosomal aberrations; dense plasma focus.

1. INTRODUCTION

In up-to-date data, circa 50-70% of oncologic patients have a need in radiation therapy (side by side with surgery, chemotherapy, hormone therapy, immunotherapy or some mixture of the five [1]). X-rays and neutron radiations fluxes here have their own special niches in cancer treatment (together with different ionizing particle beams – protons, muons, etc.), i.e. these fluxes are used for irradiation of different-type tumors positioned at various depths. In particular, neutron therapy would be prescribed for about 20% of oncologic patients provided that the selectivity of this method will be improved by 4-5 times [2]. This therapy is applied currently in about 10 medical centers in the world. Under correct patient choice and at the proper quality assurance (QA) procedures for patient dosimetry implemented at neutron therapy [2,3] the therapy allows at least 20% enhancement of direct and long-term treatment results [4].

Recently the development of new methods of neutron therapy is under way – combined neutron-capture plus X-rays and neutron-capture plus fast neutron therapy. Together with oncology a series of new applications of neutrons in various fields of clinical practice is developed. One of the most perspective lines in use of neutron radiation is a so- called boron neutron capture synovectomy, i.e. a non-surgery treatment of arthritis [5].

Isotopes, nuclear fission reactors, cyclotrons, X-ray tubes, and other-type accelerators are currently used as neutron and X-ray sources for therapeutic purposes. Although they allow large success, some important parameters are desirable to be much better (neutron

biological efficiency, dose depth distribution, stability, availability, cost, dimensions, ecological compatibility, possibility of multi-field, multi-beam and rotational irradiation, etc.). Some problems are poorly studied here. Such issues relate to dosage [6], obtained by the intermediate layers of organism when a deeply located tumor is under irradiation (surrounding tissues finding over the tumor), in particular at short neutron pulses. It is also connected with the neutron scattering and penetration within organism at the combined irradiation modes (X/gamma-rays and neutron irradiation, fast/epithermal/thermal neutron irradiation, etc.) [1].

Therapeutic efficiency of neutron radiation versus dose rate (or dose power in particular at the short-pulse irradiation) and pulse frequency is virtually not studied. In accordance with some theoretical concepts namely nanosecond (ns) and powerful pulsed radiation influence upon tumor (of the shock-like nature) may be especially effective because within such a pulse duration reparation and recovery processes have no time enough to take place, and various effects of cumulative influence and synergism are possible [7-9].

Among fundamental directions of radiation biology the study of the effects of radiation action upon enzymes were started in 60-s of the previous century [10]. Development a discipline named “radioenzymology” [11-15] as well as its branch “pulsed radioenzymology” was developed in 90-s and it occupies an important place. It is a comprehensive approach to investigate molecular mechanisms of ferment injury under effect of radicals produced while tissue's irradiation by different types of ionizing radiation. Radioenzymology is at the same time one of the most sensitive methods to determine conformational changes of molecules. For instance, radioenzymology allows determination of molecular structure and conformational state and also individual amino acid residue effect upon catalysis process at a comparable study of ferment mutant forms. It is especially important in the case when pulse duration of radiations is short compared with the reciprocal processes (e.g. with time intervals of physical-chemical, chemical or bio-chemical stages taking place at the water solutions radiolysis).

Short powerful neutron and X-rays pulses are necessary for various radiobiological tasks. Between them, for example, the determination of contribution of fast cell metabolism processes (damaged DNA reparation, oxygen effect, etc.) in the formation of the final cell and organism damages by radiation, effects of radiations of different types, spectral composition and pulse durations upon radiation injury of cells at various stages of mitosis. This work is devoted to comparative study of biophysical and radiological (radiation) responses of bio-test objects to pulsed and continuous X-ray and neutron irradiations.

2. EXPERIMENTAL DETAILS, MATERIALS AND METHODS

2.1 Apparatus

We used Sr-Y, ^{60}Co and ^{137}Cs isotopes, medical X-ray tubes and nuclear fission reactor BR-10 as *continuous* sources of X-rays and fast neutrons plus gamma-rays respectively. Alternatively as *pulsed* sources of neutrons and X/gamma-rays we applied pulsed reactor BARS-6 and Dense Plasma Focus (DPF) devices PF-5M and PF-6.

Dense Plasma Focus device is a type of plasma accelerator that produces:

- ✓ directed powerful hot (T ~ 1 keV) fast (v > 10^7 cm/s) dense (n_{pl} ~ 10^{16}…10^{19} cm^{-3}) plasma streams,
- ✓ high energy ion (E_i ~ 0.01 - 100 MeV) and electron (E_e ~ 0.01 - 1.0 MeV) beams,
- ✓ *soft* (E_{hv} ~ 0.1…3 keV), *intermediate* (E_{hv} ~ 3 …20 keV) and *hard* (E_{hv} ~ 20…1000 keV) *X-rays* and
- ✓ Fusion neutrons (E_n ~ 2.45 and 14 MeV).

These radiation types are generated in the DPF due to a number of collective effects taking place inside the plasma because of some turbulent phenomena [14].
Principle of the DPF operation is demonstrated in Fig. 1.

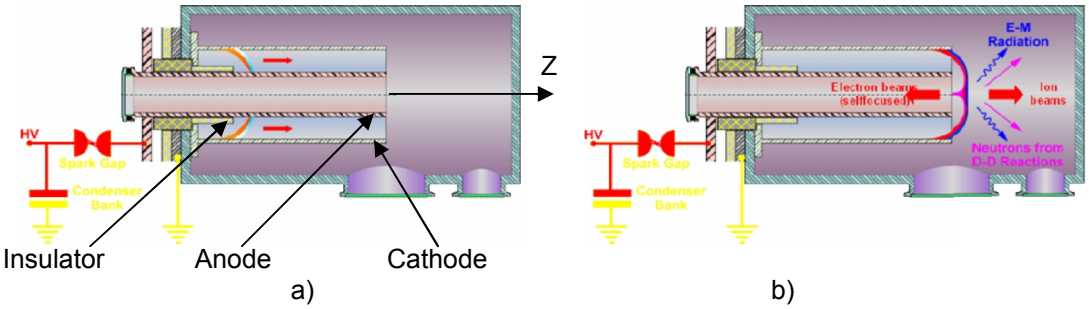


Fig. 1. Principle of operation of a DPF device: the breakdown and accelerating stages (*a*) and the implosion stage with generation of hard radiations (*b*)

In the above picture it is shown that after the initial breakdown of gas (being at a pressure of a few mbar) along the insulator a plasma-current sheath is formed. Then it is accelerated by a Lorentz force within the co-axial gap between the tube-like anode and cathode and is subsequently imploded about the axis of the DPF chamber. After the phenomenon known as the "current abruption" [16] the above-mentioned ionizing radiations are generated. In the Fig. 2 one may see two the medium-class devices (capacitor bank energies are 2 and 6 kJ for PF-5M and PF-6 correspondingly) used in these experiments.

Spectra of X-ray and gamma radiations of the sources used in our experiments were ranged (and varied) in the limits from a few keV till several MeV with peaks at about 8.047 keV (Cu K_α line in DPF) and ~ 40…150 keV (the peak of the bremsstrahlung radiation in a DPF with its position dependent on the energy of the DPF capacitor bank and on the chamber's construction) – Fig. 3 [12,17], as well as 1.17 and 1.33 MeV (^{60}Co) and 662 keV (^{137}Cs). Neutron energy was ranged from thermal till 16 MeV with peaks at 2.5 (2.7) MeV (PF-5M and PF-6, D-D fusion reaction), 1.44 MeV (fission reactors) and 14 (16) MeV (PF-6, D-T fusion reaction).

a) b)

Fig. 2. DPF devices used in these experiments: PF-5M (IMET) (*a*) and PF-6 (IPPLM) (*b*)

The dose rates (for continuous sources) and dose powers (for DPF sources and BARS reactor) were varied from 10^{-3} to 10^{9} Gy/min for neutron radiation and 10^{0} – 10^{11} Gy/min for X-rays (for DPF source) depending on the devices, radiosensitivity of biological objects and on the geometry of irradiation.

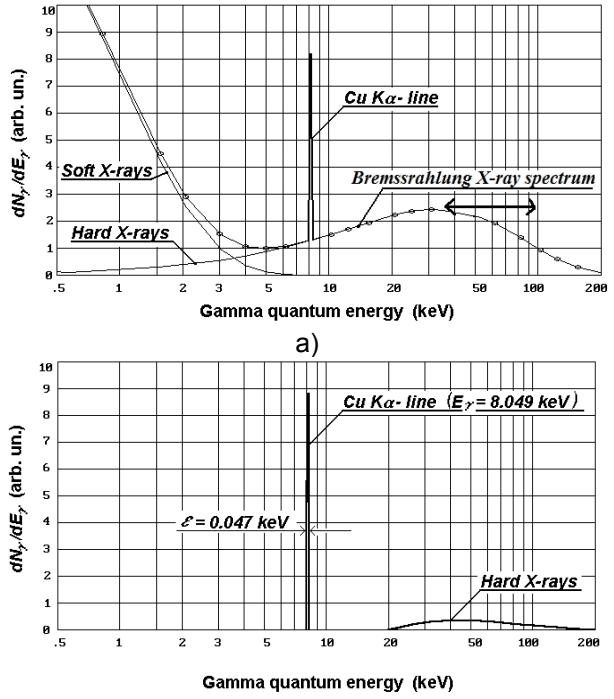


Fig. 3. The X-ray spectrum produced inside the chamber of the DPF device (*a*), and the DPF X-ray spectrum irradiated behind the 90-μm copper filter with $S_{K\alpha} / S_{Hard}$ = *5 / 1* (*b*)

Irradiations were produced by X-rays, gamma-rays and neutrons separately and in combinations. The mixed gamma-neutron character of radiation from the sources based on nuclear fission reactors (the value of $D_\gamma/D_{n+\gamma}$ was varied from 5 to 50%) has been also taken into account.

2.2 Materials

As biological test objects of different contents and complexity we used enzymes of various types (angiotensin converting enzyme, different plant peroxidases), serum, seminal fluid. These materials were obtained from companies of Russia and foreign countries (for instance, "Biozyme", U.K., "Enzymol International Inc.", U.S.A.).

If necessary, all materials were purified using original technique developed at MSU, R.F. Their activity is checked prior to experiment (for example, for ACE – by stoichiometric titration with specific competitive inhibitor–lisinopril). Concentration was determined by spectrophotometry. Thermal stability of peroxidases was studied at incubation of an enzyme (under needed concentration) at 50 and 80^{o}C in the corresponding buffer (for instance, in phosphate-borate one). Operational stability (inactivation during reaction) was calculated on the base of total curve of increased chemiluminescence obtained under optimum conditions (luminometer "Wallac 1251-002"). Preparation's homogeneity was tested by electrophoresis method in poly-acryl-amide gel in presence of potassium dodecylsulphate. In each case albumen content was determined by spectrophotometric method.

Ferment activity prior to and after irradiation was measured using spectrophotometer (Hitachi) within the wavelength range $\Delta\lambda$ = 300÷750 nm according to up-to-date techniques, for instance, for the horseradish peroxidase in relation to the following substrates: ABTS, KI, o-phenylendiamine, guayacol, phenol-antipinine probe.

2.3 Methodology

Measures on the following lines were provided during the experiments:

- ✓ Cross-correlation of the whole number of diagnostic and dosimetry devices, based on different principles and used at various installations in dissimilar conditions.
- ✓ Comprehensive (as wide as possible) use of various detectors set in each experiment.
- ✓ Measurements of as many parameters as possible in each experiment (dose, pulse duration and shape, spectrum, etc.).
- ✓ Support of experimental dosimetry by numerical mathematical modeling of interaction process (MCNP-5 and GEANT4 codes); special attention therein was paid to difference between stationary (continuous irradiation) and non-stationary (pulsed) modes (these data are not presented in this paper).
- ✓ In a course of the experiments biological test objects were irradiated in different conditions.
- ✓ Everywhere effects of the non-linear, triggering and hysteresis type were taken into account in dependence on variations of the parameters.

3. RESULTS AND DISCUSSION

3.1 Objectives/Scope of Work and Technical Approach

The ultimate objectives of the work are an elaboration of methods and equipment for diagnostics and therapy of malignant tumors based on powerful pulsed generators of neutron and X-ray radiations based on DPF devices and investigation of conditions, in which these pulsed generators can be applied. To realize the above aims the following scope of work was provided using the technical approach to obtain expected results described below:

- ✓ Elaboration and manufacturing of neutron and X-ray DPF-based generators with parameters: neutron energy – 2.5 and 14.0 MeV, X-ray photon energy – 1…600 keV, duration of neutron and X-ray pulses – 2…15 ns, neutron yield – 10^{7}…10^{11} neutrons/pulse in full solid angle, hard X-rays yield – up to 10 J/pulse in full solid angle, repetition rate of the pulses – 0.1…1.0 cps with minimal distance from the X-ray/neutron source equal to 2.5 cm.
- ✓ Development of schemes and methods of irradiation of bio-object by the above-mentioned types of radiation, generated by stationary and newly elaborated pulsed DPF-based sources.
- ✓ Working out of control-measuring and dosimetric equipment, able to operate in pulsed and stationary streams of ionizing radiation and in harsh environment.
- ✓ Gaining of new fundamental data about physical-chemical and biological influence of powerful flashes of X/gamma-rays and neutron radiations on bio-objects.
- ✓ Investigation of Relative Biological Effectiveness (RBE) of the influence of X/gamma-rays and neutron radiations upon bio-objects in dependence on parameters of their pulses.

3.2 DPF Sources of Neutrons and X-Rays

At the new devices of the type “Dense Plasma Focus” the record characteristics of dose power (*P*) were achieved. The maximal values of *P* for X-ray radiation were of the order of $10^{10\text{-}11}$ Gy/min whereas for neutrons these values were about the same as at pulsed fission reactor BARS, i.e. around $10^{8\text{-}9}$ Gy/min for the device PF-6.

This type of the sources is more ecologically acceptable compared with isotopic ones, classical high-voltage accelerators and reactor facilities. The reasons are as follows:

- ✓ They use relatively low-voltage (5…20 kV) chargers for the capacitor banks, which operate from the mains of 230 V, 6 A, 50-60 Hz.
- ✓ They become ionizing radiation sources only under electric power application (“on demand”, i.e. they are **“**push-button**”** devices).
- ✓ In the “OFF” state they are completely safe, and in contrast to isotopes they do not require special containers for storage.
- ✓ They are accident-free as against nuclear fission reactors (there is no “criticality” parameter in these devices).

In addition these DPF generators have low cost (a few orders of magnitude lower than classic accelerators), compactness and low weight (from 20 to 200 kg), small-sized irradiation chamber (a few cm), and a "record" brightness of emitted ionizing radiations.

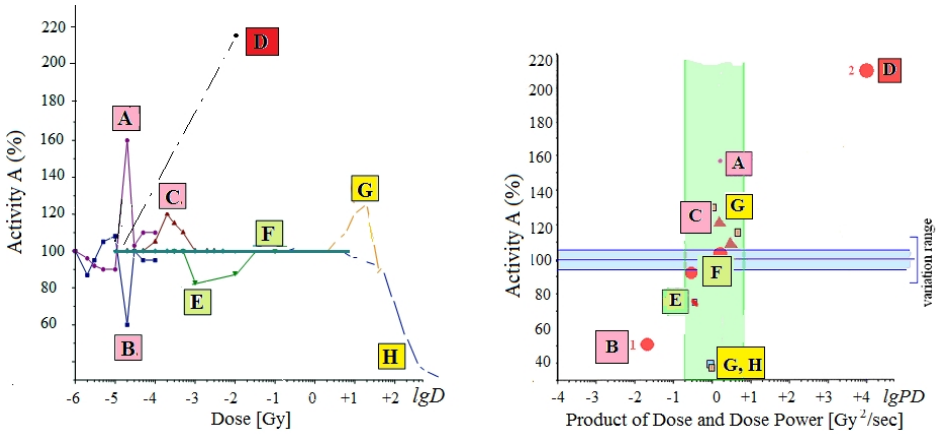
In respect to a number of parameters they are more convenient in clinic applications for diagnostics and therapy in comparison with sources commonly used at present time (fission nuclear reactors, isotope sources, high-voltage accelerators and X-ray tubes). So in principle they could in future open a series of new opportunities besides their use as the powerful neutron/X-rays source for bio-medical tests like the ones described here or in prospective therapy of cancer. E.g. it seems that they may be used in computer tomographic facility for diagnostics with source's rotation around patient, rather than patient's rotation in relation to a beam. Radiation chamber of a miniature DPF generator may be inserted inside a patient's body [17]. In some cases it provides large advantages (for instance, in stomatological panoramic X-ray photography). Portable generators, which can be powered from domestic mains or accumulator, may be indispensable in ambulance, sport medicine and field surgery. On the other hand, the development of a system consisting of a few DPF generators around patient should allow strongly optimize dose field geometry while therapy.

However because they ensure the unprecedented dose powers of X-rays and neutron radiations (due to nanosecond pulse durations) these devices must be examined with various bio-test objects for their safety in comparison with classical sources. From the other side namely this extremely high brightness of them might result in synergetic effects and open perspectives for a low-dose high-power neutron therapy of cancer. We present here some results on comparative usage of these sources applied in parallel to the classical ones in similar irradiation tests.

3.3 Radioenzymology

Somatic and testicular forms of angiotensin converting enzyme (ACE) as well as some complicated compositions (blood serum and seminal fluid) containing dissimilar concentrations of ACE at variations of conditions of an enzyme existence and on parameters of powerful pulsed and stationary sources of irradiation were investigated. Besides the short-pulsed powerful irradiation influence on different types of plant peroxidases were examined. Here we have resumed our previous works in this direction [11–15].

These experiments in certain cases have shown appearance of deviations in catalytic activity (both activation and inactivation) at super-low doses of X-ray radiation (by 4…5 orders of magnitude lower compared with the case of the isotopes' sources) but at a very high dose power (by 8…9 orders of magnitude higher than in the case of irradiations by isotopes). These results confirm our previous measurements made with other types of pure enzymes and in another conditions [9,12-15]. It is supposed that this phenomenon is ruled by a presence of the K_α-line of copper with the photon's energy $E_{h\nu}$ = 8.047 keV in the radiation spectrum, which is resonant with the absorption coefficient of metallic ions contained in the enzymes molecules, as well as by the parameter "product of dose and dose power" $D \times P$, in particular within the range of its values $D \times P \approx 0.1 \ldots 10$ Gy^2/s (Fig. 4).



a) b)

Fig. 4. Dependence of activity of enzymes on the dose (*a*) and the product of dose and dose power (*b*) at their irradiation by dissimilar sources of X-rays

A, D, C, D – DPF devices with Cu filters
E, F – X-ray tube, isotope Sr-Y, DPF devices with Al filters
G, H – isotope sources ^{60}Co *and* ^{137}*Cs*

3.4 Studies of Chromosomal Aberrations in Human Lymphocytes

It is important to take into account the absorption curves intrinsic to Cu and Al (materials of the foils screening the output window of the DPF chambers) and Ni, Zn, Co and Fe (ions of the elements presented in our enzymes under irradiation) (Fig. 5 [18]) versus the main component of the DPF photon irradiation, namely K_α-line of copper (see Fig. 3b). We used 90-μm copper foil and 2-mm aluminum foil. Observation of the data of Fig. 5 shows that this line is positioned to the left from the copper absorption edge. Also this Cu foil is thin enough compared with the foil made by aluminum. At the same time this our predominant line of luminescence of DPF can be very well absorbed by Zn and in particular by Co and Fe ions contained within the enzymes molecules due to the fact that its energy is positioned to the right from the corresponding edges of absorption.

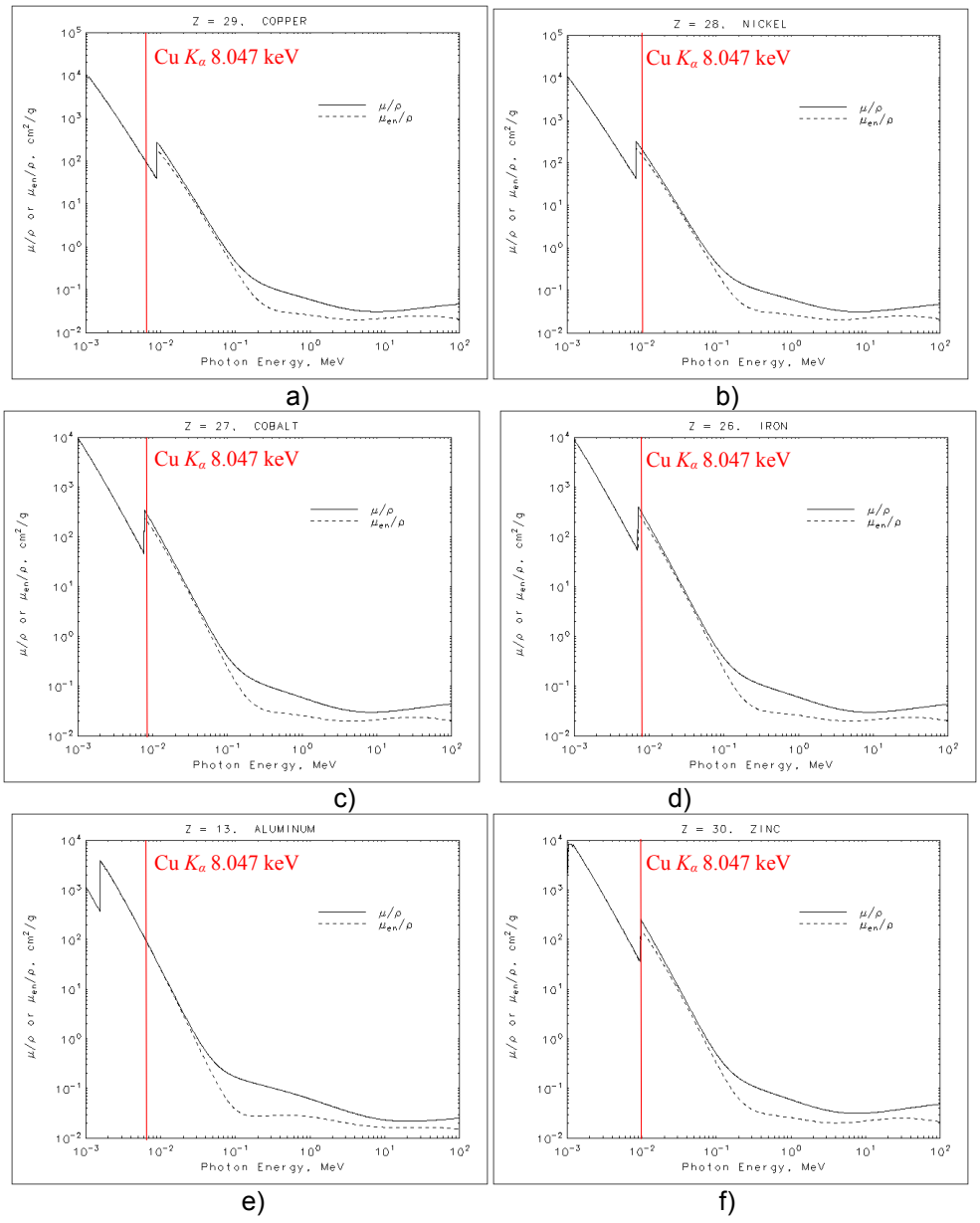


Fig. 5. Absorption curves of some elements of interest versus the most intensive luminescence of DPF through a copper K_α-line centered at the 8.047-keV energy

However at the examination of the absorption of the copper $K_{\alpha 1}$-line by ions of various elements contained in the enzyme molecules and from the other side by materials of shielding foils we have to take into account all major parameters: thicknesses (for foils), specific weight of the elements, relative positioning of their *K*-edges of absorption of the elements and in particular the mass absorption coefficients of the copper line by respective elements. All these data are presented in the Table 1 [19].

Using this information one will be able to deduce the coefficient *k* of the recalculation of the overall absorption of the Cu $K_{\alpha 1}$-line for our Cu (90 μm) and Al (2 mm) foils, which appears to be almost an order of magnitude in the favor of aluminum.

Table 1. Energy of $K_{\alpha 1}$ lines, absorption edges and mass absorption coefficients for Cu $K_{\alpha 1}$ line for a number of elements of interest

Z Element	*E* of $K_{\alpha 1}$ [Å]	*E* of $K_{\alpha 1}$ [keV]	*E* of *K*-edge of absorption [Å]	*E* of *K*-edge of absorption [keV]	Specific weight [g/cm^3]	Mass absorption coefficient for Cu $K_{\alpha 1}$ [cm^2/g]
26 Fe	1.936	6.404	1.743	7.113	7.88	308
27 Co	1.789	6.930	1.608	7.711	8.8	338
28 Ni	1.658	7.478	1.488	8.332	8.9	48.5
29 Cu	1.541	8.045	1.381	8.978	8.93	53.7
30 Zn	1.435	8.640	1.283	9.663	7.15	59.2
13 Al	8.339	1.487	7.948	1.560	2.7	50.7

Coefficient of the recalculation of the mass absorption of the Cu $K_{\alpha 1}$-line for our Cu (90 μm) and Al (2 mm) foils is as follows: k = (2000/90)(2.7/8.93) = 6.72

At the same time from this table one may see that the absorption by the enzyme's ions is about the same for Zn, Cu and Ni, whereas for Co and Fe it is about 6 times higher. Data on spectral contents and time of exposure for our sources other than DPF are as follows: X-ray tube – $E_{peak} \approx 30$ keV with $P \approx 10$ Gy/min and $\tau \sim 1$ sec.; isotope ^{90}Sr-^{90}Y – 8…2300 keV and exposure time was changed within the limits from seconds till hours with $P \sim 0.05$ Gy/sec.; isotope sources ^{60}Co and ^{137}Cs have peaks of gamma-rays at 1.17, 1.33 and at 0.662 MeV correspondingly with *P* up to 100 Gy/min and they were used with the exposure times that were changed within the limits from seconds till minutes. Our fission reactors can work in continuous and pulsed regimes. In the pulsed mode of operation the time duration of the neutron/gamma pulse was approximately 65 μsec with $P \leq 10^9$ Gy/min. In these experiments especially the dose region nearby $D \approx 10^{-4} – 10^{-5}$ Gy was marked. One may also see that quite "chaotic" oscillations seen in the picture (*a*) in the range of doses of about 8 orders of magnitude are collected in the relatively narrow "corridor" in the picture (*b*) for the product $D \times P$ occupied less than 2 orders of magnitudes.

It should be noted here that the same effect of a general nature – relative independence of materials damageability on a dose value provided that the product of the dose *D* and the dose power *P* is sustained constant – was observed at the interaction of nanosecond powerful pulses of fast ions generated by DPF with various types of steel and other solid state materials [20] during our radiation tests of elements that are counted to be perspective ones for fusion reactors.

It means that an extrapolation of results obtained with the short strong pulses may be provided for a longer interaction time observed at a lower power. It was declared that such an action may be performed using the so-called integral damage factor (IDF) *F* [21]:

$$F = P \tau^{1/2},$$

where *P* is power flux density of the irradiation beams and τ is their pulse duration. The method (certainly being very attractive) demands, however, careful investigation of the

validity of the above factor for a wide range of parameters and for different materials. Two exceptions from this basic "accumulation law" – namely points 1 ("*B*") and 2 ("*D*") in Fig. 4*b* – were obtained correspondingly: first – at the shortest pulse duration ($\tau < 2$ ns) and second – at the highest product $PD = D^2/\tau = P^2\tau = F^2$ ever achieved before. Presence of the above effects at so small doses in the conditions of a very high intensity of pulsed radiation (at nanosecond pulses) indicates the existence of peculiar (punctured) dots in the dose curves, which may pose a hazard for biological objects' functioning. Add-on neutron irradiation (at its dose powers ≤ 10^8 Gy/min) in the conditions of combined X-ray/neutron and γ/neutron fields did not show sound effects in catalytic activity changes of ACE and peroxidases, yet it was reflected in a certain amplification of them.

3.5 Studies of Chromosomal Aberrations in Human Lymphocytes

In this comparative study the cytogenetic action of neutron fission spectrum, generated by two nuclear reactors BARS-6, BR-10 and of fusion 14-MeV neutrons from PF-6 were studied with one of the test-system that is most widespread in the world – chromosomal aberrations in human lymphocytes [22,23]. Our results obtained with reactors versus ^{60}Co-source are shown in Fig. 6.

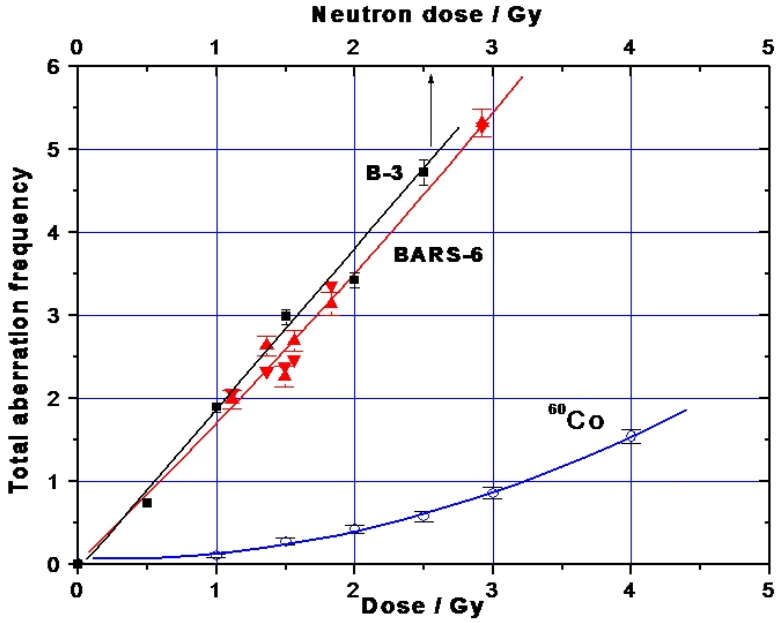


Fig. 6. Dose dependences of the total chromosomal aberration yield in human lymphocytes irradiated with the reactor BARS-6 (pulsed mode); B-3 – effect from the reactor BR-10 (continuous neutron radiation action); and the effect of irradiation by the standard isotope source ^{60}Co of γ-radiation

With the DPF device 5 plastic tubes with blood samples were placed in a cylinder plastic container near the DPF chamber (about 0.5 m apart). Diameter (inner) of the container was 55 mm, diameter of each tube was 10 mm, and wall thickness was 1 mm. Since DPF produced only 1 pulse every 10 minutes, to prevent damage reparation between pulses each container was filled with melting ice. Neutron kerma was calculated using two types of

detectors – the fission ^{237}Np detector and the activation silver detector SIVN 61. X-rays doses were measured with a 27012 clinical dosimeter (Dresden). The blood samples were received 16 pulses in total. The maximum 14-MeV neutron tissue kerma was 0.8 Gy, whereas for X-rays from DPF with spectrum extended above 40 keV it was 0.5 Gy.

Dose curves for the total chromosome aberration yields and for dicentrics yields in human lymphocytes irradiated with unfiltered mixed X-rays and neutron pulsed radiation from dense plasma focus source are presented in Fig. 7a) and b) correspondingly. For comparison some cytogenetic results obtained at continuous irradiation regime by the 14-MeV neutron generator known from literature are also shown here.

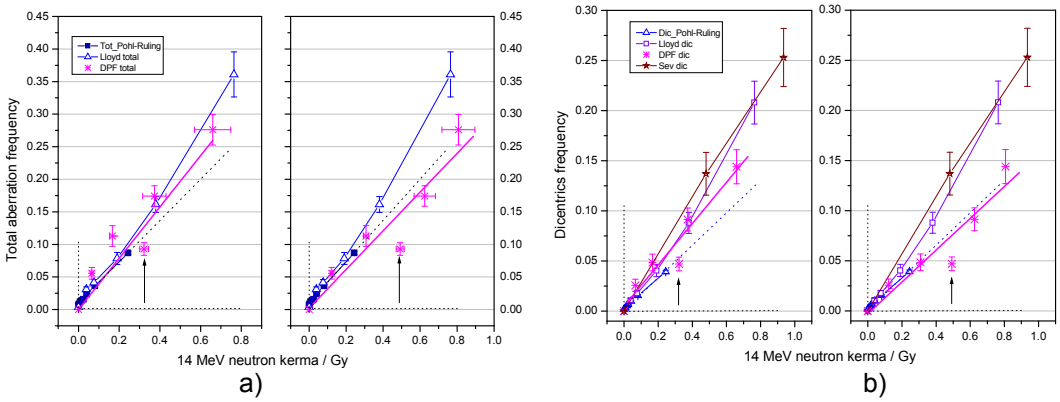


Fig. 7. (a) - Dose curves of the total chromosomal aberration yield in human lymphocytes irradiated with 14 MeV neutrons. Left panel – neutron kerma was calculated using ^{237}Np fission detector; right panel – using SIVN 61 silver detector. Linear regression equation are Y_{tot}= (0.041±0.009) + (0.36±0.022)K and Y_{tot}=(0.021±0.01) + (0.28±0.028)K, respectively. DPF – dense plasma focus. (b) - Dose curves of the dicentric chromosome yield in human lymphocytes irradiated with 14-MeV neutrons. Left panel – neutron kerma was calculated using ^{237}Np fission detector; right panel – using SIVN 61 silver detector. Linear regression equation are Y_{dic}=(0.012±0.006) + (0.21±0.026)K and Y_{dic}=(0.005±0.01) + (0.15±0.026)K, respectively

Experimental data presented in Fig. 7 were fitted to linear regression provided that one excludes from the analysis a data point marked with an arrow. As it follows from the data comparison the DPF neutron source data are closer to the data of Pohl-Ruling et al. [22] if dosimetry is based on the activation silver detector. If dosimetry is based on ^{237}Np fission detector, the experimental data are closer to those of Lloyd et al. [23]. Nevertheless, in both cases the experimental data for the DPF are within the published data for 14-MeV neutrons. At least two deductions may be inferred from the Fig. 7. First, in the experimental conditions used the major contribution to the cytogenetic effect of the DPF-based X-ray/neutron generator is made by neutrons. Second, pulsed neutron radiation of very short, nanoseconds, duration is as effective as it is at continuous mode of neutron radiation, at least, within the mutual experimental uncertainties at its relatively high values (< 10^8 Gy/min) for 14-MeV neutrons. It gives hope of applicability of DPF for the potential methods of neutron therapy instead of nuclear reactors.

4. CONCLUSIONS

These experiments were provided with a number of X-ray sources having line (discrete) and wide-range spectra extended from a few keV till 2.3 MeV and with different neutron sources having also line and wide-range spectra extended from a few eV till 16 MeV and both working either in continuous or pulse modes of operation with pulse durations from 1 ns till 100 μs we have found that in a wide range of doses and dose powers – from 10^{-5} Gy till 10^{2} Gy and from 10^{-2} Gy/s till 10^{8-9} Gy/s (for neutrons) and 10^{10-11} Gy/s (for X-rays) depending on radiosensitivity of biological test systems. As the bio-test objects we used enzymes of various types (like angiotensin converting enzyme, different plant peroxidases), serum, seminal fluid, human lymphocytes. It can be stated that:

1. With the help of well-known sources and due to implementation of newly elaborated specialized generators a complex investigation of biological effectiveness of X-ray and neutron radiations within a wide range of changes of doses, dose power and duration of action was provided.
2. During the interpretation of the experimental results, the mixed gamma-neutron character of radiation ($D_\gamma/D_{n+\gamma}$ from 5 to 50%) and neutron energy spectrum changes with distance from the radiation sources have been taken into account. Besides changes of spectrum (and of kerma correspondingly) of neutrons and X-rays in dependence of the distance from the source of these radiations and types of filters were examined.
3. As it follows from the results presented various biological systems react to neutron radiation of dissimilar dose rate (dose power) in different ways. It results from radio-biological features of their functioning. These features must be taken into consideration at the planning of neutron therapy. At the same time the range of changes of the coefficient of biological effectiveness as a rule does not go out from the limits of physiological oscillations at the neutron dose power changes with 9 orders of magnitude. I.e. it is the same for pulsed and continuous sources of neutrons.
4. As opposed to the above-mentioned neutron irradiations our experiments in the field of radioenzymology have shown that the pulsed character of action of the powerful X-ray radiation having in its spectral content a component in a close vicinity to the absorption line of metallic ion contained in an enzyme molecule under irradiation changes cardinally a response of the latter within a certain range of doses. Such an action results in activation/inactivation effects at doses differing by 4-5 orders of magnitude (to a lesser doses) compared with analogous effects obtained with low power isotope sources.
5. Listed above radiobiological characteristics of pulsed neutron and X-ray (gamma) sources indicate the reasonability of development on their base of specialized medical facilities. These devices already at present time may be used within the above-mentioned dose and dose power ranges for experiments aimed at neutron and radio therapy as well as at medical diagnostics. Due to results of the work these generators have a promising chance to substitute in future in clinical practice expensive and dangerous fission reactors, isotope sources, high-voltage accelerators and X-ray tubes used up to now.

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CONSENT

We did not work with patients.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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