DIVISION OF RADIATION AND RADIOBIOLOGICAL RESEARCH

The activity of DRRR in 2002 was concentrated on the three main directions: radiobiological research and radiation genetics, radiation research and radiation protection at the basic nuclear facilities of JINR and environment. Two first directions are included in the Topical Plan for Scientific Research of JINR as a first-priority theme. Besides, the MITRA project on development of the new radiopharmaceuticals for target therapy of human melanoma is realized in the framework of the theme.

RADIATION RESEARCH

The comparison of evaluation and experiment for nuclear cascade induced by 650-MeV protons in the core of subcritical assembly driven by the DLNP Phasotron (SAD project) is completed [1]. Preliminary work for prognostication of the radiation environment at the planned installation is started.

The investigation of the neutron yield from the extended heavy ($Z \geqslant 82$) targets under irradiation by the Nuclotron proton beams with energies of about 1 GeV is continued [2].

The estimation of the radiation efficiency of the local shields of the screpers in the 1st and 2nd sections of LAE-200 (IREN project) was carried out. The radiation parameters of a device to measure ion currents in external beams of the DC-72 cyclotron, which is being created for the Cyclotron Centre of the Slovak Republic, were done. The comparison of the neutron effective dose evaluations produced by the Monte-Carlo code and by the phenomenological method showed the acceptable accuracy of the engineering method up to 3 m shield thickness.

Activity in the framework of the FLNP and the Institute for Space Research (Moscow) collaboration concerning the Russian part of the MARS ODYSSEY project was continued. The calculation of the HEND detectors sensitivity in assembly was performed. The albedo neutron spectrum from the GSR on the spacecraft orbit as well as the albedo spectra near the Martian surface (with different mixture of water) due to GSR and ^{252}Cf radiation were evaluated.

The neutron efficiency of the thermal neutron detectors within moderators and the neutron lifetimes in them were calculated for the experiments at the powerful pulsed accelerators [3]. Part of the experimental data on the measurement of the deuteron energy distribution in $d+d \to {}^{3}\mathrm{He}+n$ reaction at ultralow deuteron collision energies was processed [4].

The calculation of some parameters of the device for identification of complex chemical substances by the nuclear physics methods was done.

The results of the comparison of different passive detector systems used for space dosimetry at the ICCHIBAN (Japan) beams of ^{4}He, ^{12}C, ^{28}Si and ^{56}Fe ions with energies of 150, 400, 490 and 500 MeV/nucleon accordingly were processed. The nuclear track detector (PADC and PETF) responses study was continued at the JINR accelerators.

Two runs of the radiobiological experiments at the Nuclotron beams (protons with an energy of 1 GeV and ^{24}Mg ions with an energy of 0.5 GeV/nucleon) were carried out.

The chromosome damage induction by low doses of radiation was studied in mammalian cells exposed to ^{12}C ions and γ rays. Determination of the shape of the dose–effect curve at the range of low doses is very important for prognoses of genetic and carcinogenic risk of radiation. Usually, for this kind of prognoses linear extrapolation of high-dose effects to low doses is used. Recently, the specific features of low radiation dose action have been demonstrated. In our experiments, complex nonlinear dose–effect dependence has been shown for induction of cells with chromosome damage [5, 6]. It is evident that the extrapolation of high-dose effects to low-dose range is incorrect.

We showed that irradiation of mammalian cells with ^{12}C ions in the dose range 1.3–40 cGy led to the decreasing number of chromosome damages below the control level. Probably this effect could be the result of repair of some spontaneous chromosome aberrations. In contrast, the number of damaged cells induced by γ irradiation exceeded the control values already at doses of 1.3–5 cGy and then increased nonlinearly with the dose. Thus, it can be concluded that inducible repair processes in cells irradiated with ^{12}C ions are switched on by lower doses and the chromosome damage repair proceeds more efficiently compared to γ rays.

The chromosome damage induced by low doses of ^{60}Co γ irradiation in human peripheral blood lymphocytes has been studied using different cytogenetic assays. Isolated lymphocytes were exposed to doses of 0.01–1.0 Gy, stimulated by PHA, and analyzed for chromosome aberrations within 48 h after irradiation by metaphase method, within 49 h — by anaphase method, within 58 h by micronucleus assay with cytochalasin B and, additionally, micronuclei were counted within 48 h on the slides prepared for metaphase analysis without cytochalasin B. Despite quantitative differencies in the amount of chromosome damage revealed by different methods, all of them have demonstrated complex nonlinear dose dependence of the frequency of aberrant cells. In the dose range 0.01–0.05 Gy the cells have shown the highest radiosensitivity; at 0.05–0.5 Gy the dose-independent induction of chromosome damage has been revealed. At doses of 0.5–1.0 Gy the dose–effect curves have become linear with the decreased slope compared to the initial one (by a factor of 5 to 10 for different criteria), reflecting higher radioresistance of cells.

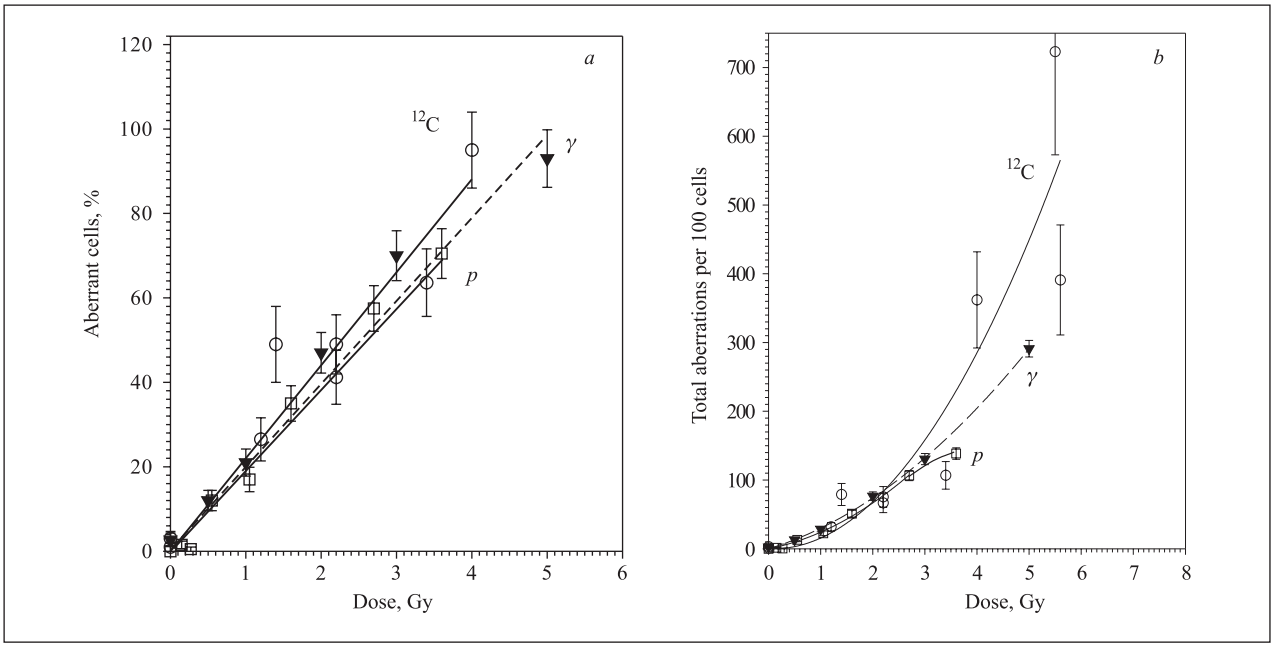
These data confirm the idea that the direct linear extrapolation of high-dose effects to low-dose range — the procedure routinely used to estimate genetic risk of low-dose irradiation — is incorrect and leads to underestimation of chromosome damage produced by low radiation doses. Similarly, the biodosimetry at doses below 0.5 Gy is not reliable (available).

At GSI (Gesellschaft für Schwerionenforschung), Darmstadt, Germany, in collaboration with Biophysics Group, the investigation of cellular response to radiation of different quality of normal healthy human tissue cells has been performed. The confluent cultures of normal human skin fibroblasts AG01522 have been used to examine the time-course of the chromosomal damage and proliferation behaviour. Nowadays this cell system is commonly used in predictive assays and radiation risk assessments based on the evaluation of chromosome damage. Cultured human fibroblasts are characterized by a limited number of cell divisions followed by terminal differentiation accompanied by the loss of proliferation capacity, senescence and death. This process of natural aging was shown to be accelerated by irradiation in the dose- and LET-dependent manner. As a first step of this process, the dose-dependent most likely permanent p53-mediated arrest state was shown to be induced in genetically damaged fibroblasts, which was regarded as a mechanism to maintain genetic integrity.

To further investigate the cellular response of normal human fibroblasts to radiation of different LET, confluent AG1522B cells were exposed to accelerated 200- and 16-MeV/nucleon carbon ions, 11-MeV/nucleon Ni ions (LET 16, 155 and 2455 keV/μm, respectively) and X rays. The chromosome damage and cell cycle progression were examined at serial time points 4-h intervals from 20 to 70 h after postirradiation receeding to low density so that essentially all dividing cells were sampled. Fluorescence-plus-Giemsa technique was applied to distinguish between metaphases of different postirradiation cell cycles.

A slight increase in the frequencies of aberrant cells and aberrations with sampling time has been found after the exposure of human fibroblasts to X rays and 200-MeV/nucleon C ions, while a more pronounced increase was detected after irradiation with 11-MeV/nucleon C and Ni ions, indicating the transient cell cycle delay of most heavily damaged cells. Moreover, for all kinds of radiation used the prominent dose-dependent decrease of mitotic activity was observed, reflecting drastic presumably permanent G_1-arrest of irradiated human fibroblasts. Using mathematical analysis based on the integration of chromosome damage over the whole time of experiment, the fraction of cells that were able to proceed to the first postirradiation mitosis within this time interval has been estimated and found to be less than 10 % of irradiated cells even after low doses of low LET radiation. With increasing dose and LET this effect became more pronounced. Hence, in all experiments only small fraction of human skin fibroblasts can be analyzed for radiation-induced chromosome damage by conventional cytogenetic techniques, in contrast to established cell lines. If the most heavily damaged cells

are preferentially arrested, the question about the representativeness of detected aberration yield with respect to entire population arises. Further experiments are in progress to address this question.



Dose-dependence of the frequency of aberrant cells (*a*) and of total chromosomal aberrations (*b*) after irradiation with protons (*p*), carbon ions ^{12}C and ^{60}Co γ rays: ○ — ^{12}C, $E = 473$ MeV/nucleon; □ — protons, $E = 1$ GeV; ▼ — γ rays

The first experiments with mammalian and human cells were performed at the beams of high-energy ions, generated by the Nuclotron [7]. Obtained data are shown on the figure for damage action of ^{12}C ions and the protons with an energy of 473 MeV/nucleon and 1 GeV, respectively, on human peripheral blood lymphocytes. There were shown no essential quantitative differences in the frequency of the cells with chromosomal damages, although the LET value of ^{12}C ions was more than 10 times higher than LET of the protons (10.65 and 0.218 keV/μm, respectively). The cytogenetical effects of both particles were also similar to those of γ rays.

The investigations of the effective radiopharmaceuticals for diagnostics and target therapy with the help of radiolabeled methylene blue (MTB) were continued [8]. The experiments with MTB labeled with ^{131}I or ^{211}At in vitro and in vivo are performed. The earlier obtained results on high accumulation of the compound in melanoma as compared with the normal tissues (4–5 times higher) were confirmed. The maximum of accumulation is reached within 2 h after compound injection.

The study of mutation induction of different nature by ionizing radiation using yeast *Saccharomyces cerevisiae* as model system of eucaryotic cells was continued. Mutagenic property of ionizing radiation was characterized by using four different mutator assays. They were a forward mutation rate assay that detects mutations inactivating the arginine permease gene (Can^r mutations) and reversion assays detecting mutations that revert a 4-base insertion in the LYS2 gene or that revert a +1T insertion in a stretch of 6 T's in the HOM3 gene. The reversion to Lys$^+$ and Hom$^+$ is due to deletion of a single nucleotide predominantly. Induction of base-pair substitutions by γ ray was studied earlier using special tester CYC1-system. Induction of AT–TA transversion in diploid yeast cells by ^{4}He ions was tested. The shape dose curve is not linear for dose 100–1000 Gy. Efficiency of ^{4}He ions with LET $=$ 80 keV/μm for induction of transversions is less than efficiencies of ^{4}He ions with LET $= 20$ keV/μm and γ ray.

The study of genetic control of DNA damage-induced arrest of cell cycle progression, named checkpoint control, was continued [9]. We intend to study interactions between the known checkpoint genes RAD9, RAD24, RAD53 and genes SRM5/CDC28, SRM8, SRM12 using such a property as radiosensitivity. We determined that CDC28 and RAD53 genes define two epistasis groups. So, CDC28 and RAD53 define two branches of the pathway controlling radiosensitivity. Interactions between these two branches and RAD52-repair pathway are under study.

The consequences of transposon Tn10 precise excision in *Escherichia coli* induced by heavy ions with different LET were studied [10–12]. Survival curves were obtained to define radiosensitivity of the cells after accelerated helium ion irradiation with LET from 20 to 100 keV/μm, and accelerated carbon ion irradiation with LET of 200 keV/μm. The dependence of the relative biological effectiveness (RBE) on LET was built. RBE maximum by the lethal action criterion was found after accelerated He ions irradiation with LET of 100 keV/μm. From the calculation of reversions in the *E. coli* gene cysC95::Tn10, the relative frequency of the precise excision as the function of the different heavy-ion irradiation doses was found, and RGE as the function of LET was obtained. Maximum of this RGE function was found on the interval from 20 to 50 keV/μm. This fact allows the conclusion that the initiation of the induced precise excision starts from the cluster DNA breaks, as also does induction of the gene mutations.

RADIATION PROTECTION

The radiation monitoring for occupational exposure at JINR nuclear facilities was carried out by the automatic systems of radiation control (ASRC) and by portable instruments. The ASRC at VBLHE, FLNR and DLNP were improved in 2002.

The experiment on irradiation of ^{252}Cf target by ^{48}Ca ions was performed in 2002 at an FLNR facility. Taking into account the high radioactivity and toxicity of the target, special steps for the radiation protection were taken. This experiment is unique for FLNR and for JINR as a whole by reason of complexity of radiation environment. The run lasted 2900 h and there was no radiation incident.

Two runs on irradiation of tritium target were conducted at the DLNP phasotron in 2002. The radiation protection and control at the experiment were realized by the DRRR and VNIIEF specialists.

The investigation of radiation environment at the Nuclotron proton beam with a current of about $2 \cdot 10^{10}$ protons per cycle showed a lack of radiation shielding in one of the experiments. As a result, the design and creation of the improved shielding near the F3 focus are planned.

In 2002 the individual dosimetry service maintained dose control to 1741 persons, including 57 visitors. The average individual yearly dose at JINR was 1.4 mSv. The maximum individual yearly dose was at FLNP (1.9 mSv).

The regular environmental monitoring of soil, plants and water from the river basins in the Dubna vicinity confirmed the conclusion that the environmental radiation pollution around JINR has remained constant for a long time and is due to natural radioactivity and products of global fallout only. Any contribution to radioactivity pollution of the environment from JINR nuclear facilities was not found. The exceeding of planned personal doses at JINR was not observed in 2002. The level of radiation protection and control at JINR corresponded to the federal rules and regularities, which was confirmed the regular inspections.

EDUCATIONAL ACTIVITY

The educational process on the specialty «Radiation Protection of People and Environment» at the chair «Biophysics» of the International University «Dubna» was continued. Ten new students were admitted in 2002. The new specialty «Biophysics of Photobiological Processes» will be established at the chair in 2003 by the initiative of Academician M. A. Ostrovsky. This specialty proposes in-depth study of the physicochemical and molecular-biological methods, the fundamentals of photophysics and photochemistry, the knowledge of laser technique, the kinetics of the initial photobiological processes in femto- and nanosecond time ranges. The specialists in this field are necessary both for research centres and for various scopes of practical activity: medicine (ophthalmology, dermatology, photochemotherapy), pharmacology, phototoxicology, biotechnology, microelectronics and others.

REFERENCES

1. *Bamblevski V. P. et al.* JINR Preprint E3-2002-273. Dubna, 2002.
2. *Hashemi-Nezhad S. R. et al.* // Nucl. Instr. Meth. A. 2002. V. 482. P. 537; 547.

3. *Boreiko V. F. et al.* // Ibid. V. 490. P. 344.
4. *Bystritsky V. M. et al.* // JINR Preprint D15-2002-200. Dubna, 2002.
5. *Shmakova N. L. et al.* // Rad. Biol. Radioecology. 2002. V. 42, No. 3. P. 245.
6. *Shmakova N. L. et al.* // Problems of Biochemistry, Radiation and Space Biology: II Intern. Symp. and II Sissakian Readings. Dubna, 2002. V. 1. P. 188.
7. *Govorun R. D. et al.* // Adv. Space Res. 2002. V. 30, No. 4. P. 885.
8. *Shmakova N. L. et al.* // Med. Radiology & Rad. Safety. 2002. V. 47, No. 3. P. 5.
9. *Koltovaya N. A., Devin A. B.* // Dokl. Akad. Nauk. 2002. V. 387, No. 6. P. 1.
10. *Zhuravel D. V.* // Vestnik Univ. «Dubna». 2002. P. 50.
11. *Zhuravel D. V., Boreiko A. V.* // Rad. Biology. Radioecology. 2002. V. 42, No. 6. P. 635.
12. *Boreiko A. V., Zhuravel D. V.* // Problems of Biochemistry, Radiation and Space Biology: II Intern. Symp. and II Sissakian Readings. Dubna, 2002. V. 1. P. 125.