Науковий вісник Ужгородського університету
Серія Біологія, Випуск 27, 2010: 193–197

УДК 57.089: 531.1.03; [57+61]: 531.1.03

COMPLEX OF INSTALLATIONS FOR EXPERIMENTAL WORKS ON NEUTRON CAPTURE SYNOVECTOMY AT KIEV NUCLEAR REACTOR

Libman V.[1], Maluk I.[1], Razbudey V.[1], Rudyk O.[1], Shevchenko Ju.[1], Tryshyn V.[1], Janch J.C.[2]

Complex of Installations for Experimental Works on Neutron Capture Synovectomy at Kiev Nuclear Reactor. — V. Libman[1], I. Maluk[1], V. Razbudey[1], O. Rudyk[1], Ju. Shevchenko[1], V. Tryshyn[1], J.C. Janch[2]. — *Installations for (a) irradiation of biological samples and (b) analysis of content of neutron capture nuclides including ^{10}B were created at two horizontal channels of Kiev research nuclear reactor. Neutron spectra at the outlets of the beams from the channels were formed with neutron filters placed inside the channels. Neutron flux density distribution was investigated in the irradiate chamber. A phantom of a human knee joint was manufactured for investigating neutron fields inside biological tissues. Its elements consist of materials which have neutron-physical characteristics similar to real joint tissues ones. Boron was included in the elements simulating synovial tissue and the joint cavity. 41 diminutive activation detectors of Mn were placed in all elements of phantom: "skin", "synovium", "joint cavity" and "bones". Activation measurements with phantom on the beam had indicated that therapeutic dose of 100 Sv could be accumulated for 30 minute in tissues with content of ^{10}B about 0.35%. At that a dose in tissues not containing boron did not exceed 0.6 Sv, what is acceptable for cartilage tissues.*

Key words: *neutron capture synovectomy, nuclear reactor, irradiation, neutron beam, Monte Carlo Method.*

Address: *[1]– Institute for Nuclear Research, NAS of Ukraine (47, Prospekt Nauki, Kiev, 03680); [2] – Massachusetts Institute of Technology (150, Albany Street, Cambridge, Massachusetts, USA 03139).*

Комплекс установок для експериментальних досліджень по нейтроно-захватної синовектомії на Київському реакторі. — В. Лібман[1], И. Малюк[1], В. Разбудей[1], А. Рудик[1], Ю. Шевченко[1], В. Тришин[1], Ж. Янч[2]. — *На двох горизонтальних пучках Київського дослідницького реактора створені установки для досліджень по нейтроно-захватної синовектомії: (а) для опромінення біологічних об'єктів та (б) визначення вмісту нейтронопоглинаючих ізотопів у біологічних зразках. Спектри нейтронних пучків на виході з каналів формувалися нейтронними фільтрами, розташованими у горизонтальних каналах. Для дослідження нейтронних полів у тканинах суглоба був виготовлений фантом колінного суглобу людини. Його елементи зроблені з матеріалів, що мають нейтронофізичні характеристики, близькі до характеристик тканин реального суглоба. У елементи, що імітують синовіальний шар і суглобову капсулу був введений бор. Мініатюрні активаційні детектори були розміщені в усіх елементах фантома: у "шкірі", "синовіальному шарі", "суглобовій капсулі" і "кістках". Загалом 41 детектор. Вимірювання на нейтронному пучку показали, що терапевтична доза 100 Зв у тканинах з вмістом ізотопу ^{10}B 0.35% по масі може бути накопичена за 30 хвилин. При цьому у тканинах, які не містять бор, доза не перевищує 0.6 Зв, що прийнятно для тканин суглоба.*

Ключові слова: *нейтроно-захватна синовектомія, ядерний реактор, опромінення, нейтронний пучок, метод Монте-Карло.*

Адреса: *[1] – Інститут ядерних досліджень НАН України (47, Проспект Науки, Київ, 03680); [2] – Масачусетський технологічний інститут (150, Албані Стрит, Кембридж, Масачусетс, США, 03139).*

Introduction

Neutron Capture Synovectomy was proposed as a method of treating Rheumatoid Arthritis (RA) patients [1]. RA is a painful infectious illness that affects joints. While RA an interior membrane of articular cavity becomes inflamed, synovium becomes thicker up to 0.5–1.5 cm (normal 1–2 cell layers). Autoimmune reaction of synovial sells results in discharging ferments which destroy joint tissues up to deprivation of function. RA elapses painfully and often is a reason of disability. About 2% of population suffers from this disease, and usually conservative treating is not effective. An ordinary method of treating is surgical ablation of overgrown synovium. The surgery is very traumatic, and, as a rule, a relapse happens in 2–5 years. A radiation synovecnomy is an alternative method [2,3] when synovium is destroyed by β-radiation of radioactive liquid inserted in a joint. A drawback of this method is a possible proliferation of radioactivity over the organism through lymph and blood streams. For this reason radiation synovectomy is prohibited in some countries, for example in USA.

NCS is a method, which unlike surgical synovectomy, is not highly traumatic and unlike radiation synovectomy does not require administration of radioactive substances in patient's organism. The idea of the method is destroying a pathologic synovium tissue by products of reaction of neutrons with ^{10}B:

$$^{10}B + n \rightarrow {}^{7}Li\ (0.84\ MeV) + {}^{4}He\ (1.47\ MeV) + \gamma\ (0.478\ MeV).$$

A substance that contains ^{10}B and can be accumulated selectively in synovium, so called neutron capture agent (NCA), is administrated into a cartilage capsule.

The above reaction is very probable (cross section is of 3840 barn for thermal neutrons). The first two reaction products, ^{7}Li and ^{4}He, have a short range (less 10 μm), thus on the order of biological cell size. In the most part of reactions this results in the energy depositions just inside the cells where ^{10}B is accumulated, i.e. inside the pathological synovium tissue, and destroys it.

Though NCS is based on the same principles as neutron capture therapy (NCT), the method of treatment of brain tumor [4], there are some essential distinctions that are connected with anatomic and physiologic distinctions between joints and brain. Firstly, tissues that are irradiated in NCS are located relatively near to the joint surface, whereas tumors in brains are located deeply, up to 8 cm. Secondly, direct injection of boron containing compounds into a joint is possible, therefore much higher content of boron is achievable in synovium than in malignant tissues of brain. Thirdly, joints are located far from vital organs, and they are less radiosensitive than brain. Fourthly, wide neutron beams, which irradiate joint as a whole, are suitable for NCS, whereas NCT needs narrow beams because only small part of head must be irradiated. Fifthly, it is much more difficult to fulfill the requirements of selectivity in NCT because malignant and normal cells are cells of the same type, whereas in NCS synovial tissue essentially differ from others articular tissues. Therefore, more possibilities can be achievable for selective accumulation of NCA in synovium, than in malignant cells of brain. All this, from one hand, simplifies choice of boron carrier in NCS, and, from other hand, does possible to create a neutron source for NCS at such nuclear installations where creation of sources for NCT is very difficult by technical or economical reasons.

Irradiating installation

The irradiating installation for NCS investigations that were carried out by researches of USA [1, 5, 6] was developed at 4.1 MeV deuteron accelerator with current on Be target 1 mA. Since there are no accelerators with such high current in Kiev, a possibility to create the installation on the base of 10 MW Kiev research nuclear reactor, which is a powerful source of wide energy diapason neutrons, was considered.

As it was shown [4], "intermediate" neutrons of 1 eV – 20 keV are the most suitable for destruction of pathological tissues in organism (malignant tumors, hypertrophied synovial shells) with NCT method. Lower energy neutrons (so called "thermal" neutrons) penetrate practically not deeper 1 cm. "Fast" neutrons (E>20 keV) result in overradiation of joint's skin because of high energy recoil protons. Highly intensive sources of intermediate neutrons at thermal reactors are created by means of translation of their thermal columns into material compositions that moderate and filtrate neutrons [7, 8], sometimes with use of a converter on the base of fissionable nuclides [9–10]. Previously it was shown the possibility of creating such a source at the thermal column of Kiev reactor [11]. But this requires considerable funds and therewith some changes in reactor construction. The required changes do not touch the core, but Kiev reactor is located inside the city boundaries, and even insignificant intervention in its construction and operating mode is very undesirable. As it was shown [12], thermal neutrons are also suitable for NCS if to use beams with a large cross section. In such beams neutrons penetrate into the depth of location of synovial membranes by multiple scattering. Removal of fast neutrons from reactor beam is possible by application of single-crystal filter, which is to place in the beam before irradiating chamber. Briefly, the influence of single-crystal filter on beam means, on one hand, effective decrease of fast neutron flux and, on the other hand, almost free transmission of thermal neutrons as a result of coherent interaction with crystal structure. Therefore, it is possible to reduce considerably the undesirable irradiation of skin with above-thermal neutrons.

Construction of the irradiating installation for researches in NCS was developed and performed basing on forerunning calculations. It consists of such blocks (Fig. 1):

– Research nuclear reactor as a source of primary neutrons,

– Neutron filter placed in the 5th channel shutter,

– Chamber for irradiation of biologic objects,

– Radiation shielding and trap of neutrons and gamma rays.

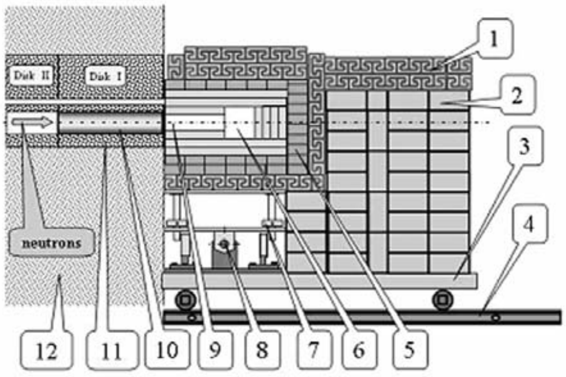

Fig. 1. Irradiating installation: 1 – shielding of borated polyethylene, 2 – shielding of cast iron, 3 – main cart, 4 – rail, 5 – shielding of lead, 6 – irradiating chamber, 7 – adjustable cart, 8 – drive of the adjustable cart, 9 – axis of the beam, 10 – neutron filter (single-crystal of silicone), 11 – channel's shutter, 12 – biologic shield of reactor

Рис. 1. Опромінювальна установка: 1 – захист з борованого поліетилену, 2 – захист з чавуну, 3 – головний возик, 4 – рейка, 5 – захист з свинцю, 6 – опромінювальна камера, 7 – регульований возик, 8 – привод регульованого возика, 9 – вісь пучка, 10 – нейтронний фільтр (монокристал кремнію), 11 – шибер каналу, 12 – біологічний захист реактору

Reactor. Kiev research reactor was put into operation 49 years ago. After modernization that was completed in 2008 its service life was prolonged up to 2015. Now it is ready to operate on low enriched fuel (19.8% of ^{235}U). Rated thermal power is 10 MW. Neutron flux density in the core is about 10^{14}, at the horizontal channels outlets 10^9 neutron/cm^{2}s.

Neutron filter. The filter is made of single-crystal silicon. It is high-quality material for thermal neutron filter because silicon nuclei have low both capture and incoherent scattering cross sections. Crystal with the size Ø94.3×400 mm had been grown, enclosed into a thin-walled frame of stainless steel and mounted in the threaded socket of the channel shutter.

Irradiating chamber (IC). IC is a tetragonal prism of polyethylene with two sockets for samples and additional filter. Its walls thickness is 8 cm. The chamber is mounted on metal table; its position can be continuously adjusted in vertical and horizontal directions. It is covered with shielding materials: lead, borated polyethylene, cast iron, blocks filled with iron scrap and solution of boric acid. Together with shielding the chamber is placed on a steel platform that can roll away on arc-like rails (so an access to the channel outlet can be opened). The total mass of the installation is about 10 T.

In accordance with measurements, all dose levels around the installation exceed neither national standards nor control levels at Kiev reactor.

Measurements of neutron beam parameters. Method of activation detectors was used for neutron field investigation. Thin (0.1–0.4 mm) plates of Mn were used as detectors. Their masses did not exceed 0.1 g, time of irradiation – 1 hour, time of activity measurement – 2 minutes. The measurements were carried out on gamma-spectrometer with HPGe detector. The statistical errors did not exceed 1%.

A "computer experiment" using Monte Carlo code MCNP-4C [13] ever simulated the real one. Such "experiment" gives an opportunity to calculate fluxes, activity of Mn, dose rate and many other values in any point of the experiment space. After comparison of these calculated values one with others and with experimental values of Mn activity it is possible to obtain their "experimental-calculated" values.

By this method densities of neutron fluxes were determined both with filter and without it in three positions of the channel outlet: on the beam axis and 3.5 cm to the left and right. Besides, additional measurements were carried out when the beam was blocked with 0.5 mm Cd disc. This gave opportunity to determine not only the neutron flux, but its low (<0.5 eV) and high (0.5–20000 eV) energy components. The beam parameters are presented at the Table 1. As it is seen from the table 1, calculated Mn activation reaction rate and neutron flux density are in agreement with experimental values (discrepancy not more than 10%).

Table 1. Beam parameters

Таблиця 1. Параметри пучка

Presens of Si filter	**Position of detector**	**Mn activation reaction rate, MBq/g**		**Neutron flux density, 10^8 n/cm^{2}s**		**Cd relation**	
		Measured	**Calculated**	**Measured**	**Calculated**	**Measured**	**Calculated**
No	on the axis	70.7	74.5	9.5	10.0	14.9	32.6
	3.5 cm to the left	66.8	74.5	8.9	10.0	14.0	32.6
	3.5 cm to the right	68.6	74.5	9.2	10.0	14.3	32.6
Yes	on the axis	23.7	26.0	1.92	2.11	126	258
	3.5 cm to the left	22.8	26.0	1.85	2.11	128	258
	3.5 cm to the right	22.7	26.0	1.84	2.11	129	258

This shows rather good accuracy of calculation model. With respect to Cd relations, calculated values are twice higher than measured. We consider that additional "poisoning" the Be reactor reflector with ^{3}He may be the reason of the discrepancy. This was possible as for 2 years before the measurements reactor did not operate, and some quantity of ^{3}He were created from decay of tritium which accumulated during operation of the reactor in previous years. It is probably that in future after 2 week operating of the reactor ^{3}He will burn out and Cd relation will increase.

Distribution of neutron flux density inside the IC. A composition of 57 samples of Mn fixed on Al disc (Fig. 2) was irradiated in IC. The activity of every sample was measured separately. In common they gave a picture of neutron flux density distribution over the plane perpendicular to the beam (Fig. 3).

Investigation of neutron field inside human knee joint phantom. A phantom is an artificial object in which radiation fields like a field in a real joint are formed in the beam. Soft tissues contain substantially organic component and water. Neutron field distribution in a joint becomes formed essentially by atoms of hydrogen that have a record high scattering cross section. Frequently in works, related to NCT, biological objects are modeled with phantoms of water. However, joints in NCS include bones and tissues with neutron-absorbing admixtures (B or Gd). Therefore, we manufactured the phantom of more complex construction (Fig. 4). Identity of neutron fields in the phantom was tested by Monte Carlo calculations. Two input files for MCNP code with geometry of performed phantom were worked out when it is filled with: (a) materials of the performed phantom and (b) biological materials close to tissues of a real joint.

Element compositions of skin and bone were taken from [14]. Composition of synovium was like skin, the volume of joint cavity was filled with water, but the same quantities of boric acid (0.35% of ^{10}B), as in the made phantom, were added into both volumes.

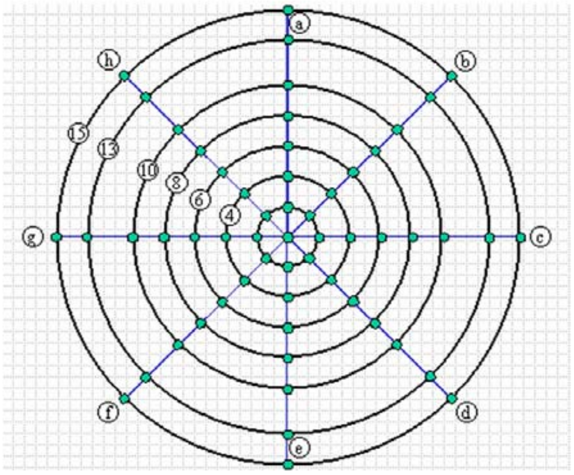

Fig. 2. Placement of Mn samples for determining neutron flux density distribution in the irradiating chamber

Рис. 2. Розташування зразків марганцю для визначення розподілу щільності нейтронного потоку в опромінювальній камері

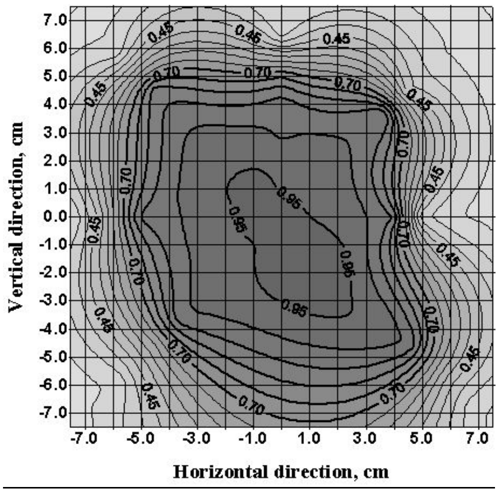

Fig. 3. Neutron flux density distribution in the irradiating chamber, relative units

Рис. 3. Розподіл щільності нейтронного потоку в опромінювальній камері, відносні одиниці

Table 2. Mn activation reaction rate and equivalent dose rate in phantom

Таблиця 2. Швидкості реакції активації Mn та потужності еквівалентних доз у фантомі

Element of phantom	Mn activation reaction rate, MBq/g	Equivalent dose rate, rem/hr	Element of phantom	Mn activation reaction rate, MBq/g	Equivalent dose rate, rem/hr
Skin at the front	21.10	114	Synovium behind	0.28	634
Skin at the left	3.23	46	*Femur* at the front	7.66	77
Skin at the right	3.27	44	*Femur* at the center	1.8	76
Skin behind	0.53	16			
Synovium at the front	16.40	21200	*Tibia* at the front	11.60	122
Synovium at the left	1.42	3120	*Tibia* at the center	3.62	101
Synovium at the right	1.45	3170	*Tibia* at the right	8.40	55

Comparison of results of equivalent doses calculations showed that doses in the performed phantom represented doses in a phantom of biological materials with discrepancies not more than 30%.

Evaluation of radiation doses in the performed phantom. 41 activation detectors of Mn were placed over the phantom volume that was irradiated in the IC. The activities of irradiated Mn samples and obtained from them activation reaction rates were the values that were recorded directly in experiment. Both reaction rates and equivalent doses were calculated in parallel "computer experiment" simultaneously. Comparison of calculated doses with calculated and experimental reaction rates did possible to get "experimental-calculating" values of doses. Of course, those are only estimated data, but they are more reliable than simply calculating ones because they are based on the reaction rates measured in various points of phantom. The results of measurements and estimated equivalent doses are presented in the Table 2.

Installation for determination of Boron and other elements in biological samples

The second installation related to NCS was developed on another horizontal channel (№7). It is an installation for determination of Boron and other elements in

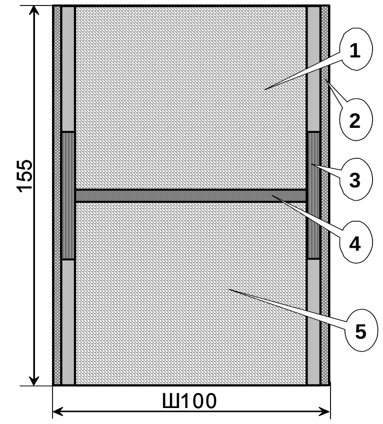

Fig. 4. Phantom geometry and materials: 1 – "*femur*" (alabaster), 2 – "skin" (water), 3 – "pathological synovial shell" (paraffin + boric acid,10.9%), 4–"joint cavity" (paraffin + boric acid 10.9%), 5 – "*tibia*" (alabaster)

Рис. 4. Геометрія фантому та матеріали: 1 – "стегнова кістка" (алебастр), 2 – "шкіра" (вода), 3 – "патологічна синовіальна оболонка" (парафін + борна кислота, 10.9%), 4 – суглобова сумка (парафін + борна кислота, 10.9%), 5 – "велика голінна кістка" (алебастр) biological samples. It operates by a method that is used widely, for example [15]: quantity of Boron in the sample that is placed in collimated neutron beam is determined by means of prompt γ-quanta of 0.478 MeV, which are recoded with HPGe coaxial detector, placed aside from the beam. The sensibility of ^{10}B determination is about 1 ppm for 3 hours of measurement.

Conclusion

Firstly in Ukraine and the secondly in the world installation for experimental irradiation of biological objects, related to investigations in neutron capture synovectomy, was developed at Kiev research nuclear reactor. The neutron field in the irradiating chamber has parameters suitable for therapeutic irradiation, for example, for treating patients, suffering from Rheumatoid Arthritis. Therefore, it may be considered as a prototype of a medical installation.

An installation for determination of contents of nuclides, important in neutron capture synovectomy, for example ^{10}B, was developed also.

Thus, conditions for investigations in physics, biology, chemistry and medicine related to neutron capture synovectomy, had been created in the Ukraine.

The work was supported by U.S. Civilian Research and Development Foundation.

1. *Yanch J. C., Shortkroff S., Shefer R. E.* et al. Treatment of Rheumatoid Arthritis Based on the ^{10}B(n,α)^{7}Li Nuclear Reaction // Med. Phys, 1999, vol. 26, p. 364 – 375.
2. *Deutsch E., Brodack J. W., Deutsch K. R.* Radiation Synovectomy Revisited // Eur. J. Nucl. Med., 1993, Vol. 20, p. 1113 – 1127.
3. *Johnson L. S and Yanch J. C.* Absorbed Dose Profiles for Radionuclides of Frequent Use in Radiation Synovectomy // Arthritis and Rheumatism, 1991, vol. 34, p. 1521 – 1530.
4. *Current Status of Neutron Capture Therapy*, IAEA–TECDOC–1223, Vienna, 2001.
5. *Gierga D. P., Yanch J. C., Hefer R. E. Blackburn B. W.* Construction of an Accelerator–Based Neutron Beamline for Treatment of Arthritic Joints, in "Frontiers in Neutron Capture Therapy", (Hawthorne M. F., Kenneth S., and Wiersema R. J. Eds), 1998, vol. 1, Kluwer Academic/Plenum Publishers, New York, p. 461 – 467.
6. *Yanch J. C., Shortkroff S., Shefer R. E., Gierga DBinello., E., Zhu X., Jiang H.* Development of BNCS for the Treatment of Arthritic Disorders, in: Sauerwein W., Moss R., Witting A., eds.: "Research and Development in Neutron Capture Therapy". Proc. of the 10th International Congress on Neutron Capture Therapy, Essen, Germany, 2002, Monduzzi Editore, International Proceeding Division, p. 1007 – 1012.
7. *Nigg D., Wemple C., Venhuizen J.et al.* Initial Neutronic Performance Assessment of an Epithermal Neutron Beam for Neutron Capture Therapy Research at Washington State University, Development of BNCS for the Treatment of Arthritic Disorders, in: Sauerwein W., Moss R., Witting A., eds.: "Research and Development in Neutron Capture Therapy". Proc. of the 10th International Congress on Neutron Capture Therapy, Essen, Germany, 2002, Monduzzi Editore, International Proceeding Division, p. 135 – 139.
8. *Auterinen I., Hiismaki P., Seren T., Seppala T.* Creating of Epithermal-Neutron Field for BNCT Using a TRIGA Reactor and Aluminum Fluoride Composite as Neutron Moderator, in: Proceedings of the Conference "Technology for New Century", April 19 – 23, 1998 ANS 1988, vol. 2, p. 37 – 83.
9. *Rorer D., Patti F., Ma R. et al.* Upgrade of the Epithermal Neutron Beam Using ^{235}U Fission Plates at Brookhaven Medical Research Reactor, in: "Frontiers in Neutron Capture Therapy", (M. F. Hawthorne, Wiersema R. S., and R. J. Eds), 1998, vol. 1 Kluwer Academic/Plenum Publishers, New York, p. 283 – 288.
10. *Harling O. K., Riley K. J. et al.* The Fission Converter-Based Epithermal Neutron Irradiation Facility at the Massachusetts Institute of Technology Reactor // NSI, 2002, vol. 140, p. 223 – 240.
11. *Gritzay O. O., Kalchenko O. I., Razbudey V. F. et al.* Monte-Carlo Calculations for the Development of a BNCT Neutron Source at the Kyiv Research Reactor // Applied Radiation and Isotopes, 2004, v. 61, Issue 5, p. 869.
12. *Berlizov A. M., Razbudey V. F., Shevchenko Yu. B., Tryshyn V. V.* Prospects of Neutron Capture Synovectomy at Thermal Nuclear Reactors // Nuclear Physics and Atomic Energy, 2006, № 1, p. 67 – 72.
13. *Briesmeister J.F.*, ed., "MCNP–A General Monte-Carlo N-Particle Transport Code", version 4C, Los Alamos National Laboratory Report LA-13709-M, 2000.
14. *American National Standard ANSI/ANS* – 6.1.1 – 1977.
15. *Harling O. K., Chabeuf J.–M. et al.* A Prompt Gamma Neutron Activation Analysis Fasility Using a Diffracted Beam // Nuclear Instrument and Methods in Physical Research, B, 1993, vol. 83, p. 557 – 562.

Отримано: 10 листопада 2009 р.
Прийнято до друку: 4 лютого 2010 р.