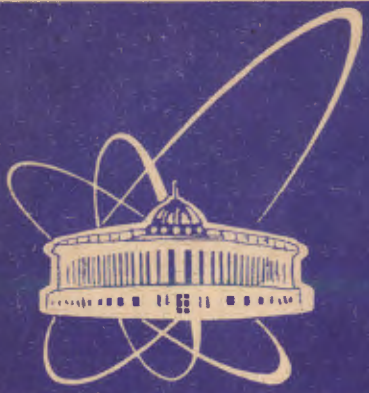

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DOSE-STOCHASTIC RADIOBIOLOGICAL EFFECT RELATIONSHIP IN MODEL OF TWO REACTIONS AND ESTIMATION OF RADIATION RISK

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1. INTRODUCTION

The search for the dose-effect relationship began many years ago [1-8]. However, the problem of possible consequences of radiation exposure in humans, particulary by low doses, is far from its decision [9]. The striking illustration of undecision of the problem is two mutually exclusive predictions of consequences of radiation exposure in humans in the Chernobyl accident [10,11]. One of them prophesies about 300000 lethal outcomes from cancer in result of the Chernobyl accident [10]; the second informs about prevention of 20000 lethat outcomes from cancer in the ex-USSR republics [11]. Another illustration is connected with 1990 Recommendations of the International Commission on Radiological Protection [12]. The ICRP has considered the dose limits insufficiently low and recommended to reduce them, while a number of specialisis considers this recommendation as unjustified and extravagant; furthermore the author [13] has considered ICRP recommendation as speculative because of danger to the human health. These two illustrations are consequence of that the authors of the predictions, opinions and recommendations have used different dose-effect relationships. In this connection a search of new more effective dose-effect relationships may be justified and actual.

This article presents such new dose-stochastic radiobiological effect relationship, demonstrated its possibility to fit some of the most striking control results and gives the estimation of radiation risk at the Joint Institute for Nuclear Research based on the model of two defence reactions (TDR).

2. MODEL BASE

The main considerations and conditions, assumed as basis of the TDR model, and formulas are following: 1) Radiobiological effects, which are the result of random events, are examined; 2) Biological objects may be any capable of self-defence organisms; 3) A defence system is realized in two types of organism reaction (response), which determine innate μ_n and adaptive μ_a radiosensitivities; 4) The significances of μ_n are determined by host (inner) factors; and the significances of μ_a, by external factors; 5) The possibilities of adaptive reaction

are determined by the coefficient of capabilities of defence system ν; 6) An ionizing radiation exposure decreases or increases the frequency F or probability W of effect unsurely creating new species of it — radiation induced. The considerations 3—6 need in argumentation, which partly may be adopted from the published studies with cells [15,16] and partly may be supported in success fitting of experimental results and control. For higher organisms it is determined that response of immune system on the action of any dangerous factors sums up two components — innate and adaptive, divided by some time interval [17].

3. FORMULAS OF TDA MODEL

We assume a function f as a basis of dose-effect relationship and define it thus that the product $(1 - W_c)f$ is the probability to avoid stochastic effect at dose exposure H; here W_c is the probability of the effect in control (probability of spontaneous effect, back-ground). Then the probability of the effect is

$$W = 1 - (1 - W_c)f. \tag{1}$$

The excess of the effect above background is the difference of W and W_c:

$$\Delta W = W - W_c = (1 - W_c)(1 - f). \tag{2}$$

The relative risk (RR) is determined as a ratio

$$RR = \frac{W}{W_c} = \frac{1 - (1 - W_c)f}{W_c}. \tag{3}$$

The mean frequency of expected effect in accordance to [8] and (1) is

$$F = \ln \frac{1}{1 - W} = \ln \frac{1}{(1 - W_c)f}. \tag{4}$$

A function f is found by solving the following differential equations:

$$df_n = -\mu_n f_n dH, \tag{5}$$

$$df_a = (\mu_n \nu f_n - \mu_a f_a)dH. \tag{6}$$

Here f_n is the fraction avoided effect (lesion) of individuals because of the innet defence reaction at radiosensitivity μ_n, f_a is the additional fraction avoided

effect of individuals because of the adaptive defence reaction at radiosensitivity μ_a, and ν is the coefficient of capability of a defence system. The solution is received for two particular cases that may help to describe control results adduced in part 4. In the first case significances of μ_n, μ_a, ν are considered as independent of H, then the solutions are [14]

$$f_n = \exp(-\mu_n H), \tag{7}$$

$$f_a = \frac{\nu\mu_n}{\mu_n - \mu_a}[\exp(-\mu_a H) - \exp(-\mu_n H)]. \tag{8}$$

Total fraction avoided effect (lesion) of individual is considered as a sum of f_n and f_a:

$$f = \exp(-\mu_n H) + \frac{\nu\mu_n}{\mu_n - \mu_a}[\exp(-\mu_a H) - \exp(-\mu_n H)]. \tag{9}$$

In the second case, μ_n is considered as independent of H; and μ_a and ν, as dependent on H, then the solution for f_a is (7) and is described by the equation

$$f_a = \exp\left(-\int_0^H \mu_a dH\right)\left\{\mu_n \int_0^H [\nu \exp(-\mu_n H) \exp\left(\int_0^H \mu_a dH\right)]\right\}. \tag{10}$$

In all cases the significances μ_n, μ_a, ν have to satisfy the condition

$$f \le \frac{1}{1 - W_c}. \tag{11}$$

The analysis (9) at the condition (11) shows the possibility of describing a hormesis [11,18,19], as f may be more than 1, and $W < W_c$ at $\nu > 1$. At low doses, when $\mu_n H << 1$, we may get Eq.(12) if restrict the first two terms of expansion in the row of exponents:

$$f = 1 + \mu_n(\nu - 1)H. \tag{12}$$

Substituting this value f into (2), we have

$$\Delta W = (1 - W_c)(1 - \nu)\mu_n H \tag{13}$$

and for derivative

$$W' = \Delta W' = (1 - W_c)(1 - \nu)\mu_n. \tag{14}$$

Formula (13) shows that absolute excess of risk is straightly proportion to dose at low-dose and above-mentioned conditions. In this case for the derivative $\Delta W'$ ICRP recommends the name — «probability coefficient for stochastic effects». From (14) one can see that the significances of $\Delta W'$ may vary in a wide range, that was noted in the study [9]. Negative significances ΔW and $\Delta W'(\nu > 1)$ correspond to hormesis.

4. MODEL VERIFICATION

At present time, a verification of right and effectiveness of considerations, assumed as the basis of the TDR model, may be only in an ability of fitting different observed dose-effect relationships with the help of the formulas presented in part 3. In the capacity observed quantities in the epidemiological control, W and RR are selected, furthermore f and F — in the experiments with cells.

4.1. Epidemiological Results

The relative risk of cancer mortality for Japanese A-bomb survivors in Horishima and Nagasaki is presented in Fig.1.

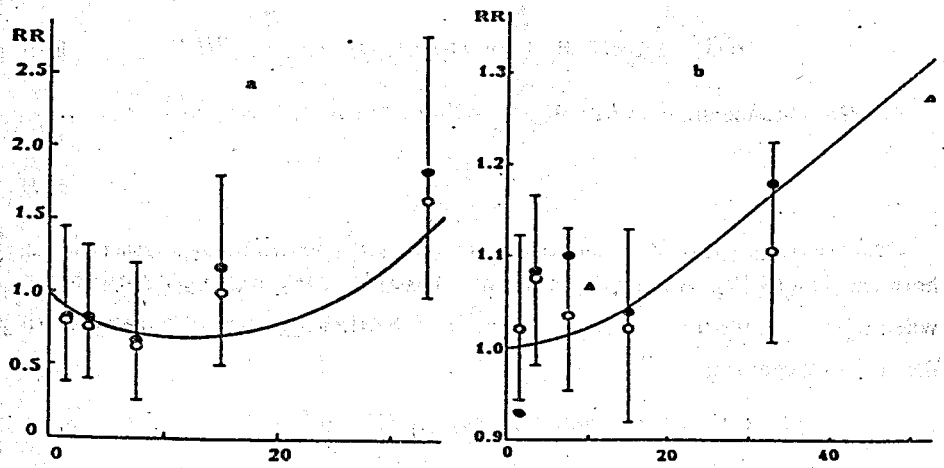

Fig.1. Relative risk RR of A-bomb survivors: a) mortality from leukaemia; b) mortality from all cancer other than leukaemia; •, △, o — epidemiologogical studies results on all of survivors (•[18], △ [20]) and those who were less than 40 years old at the time of bombing (o — 95% confidence interval [18]),'——— — TDR model result

The TDR model results are obtained by formula (3); which parameters have been determined at the consent condition of calculation and control results; they

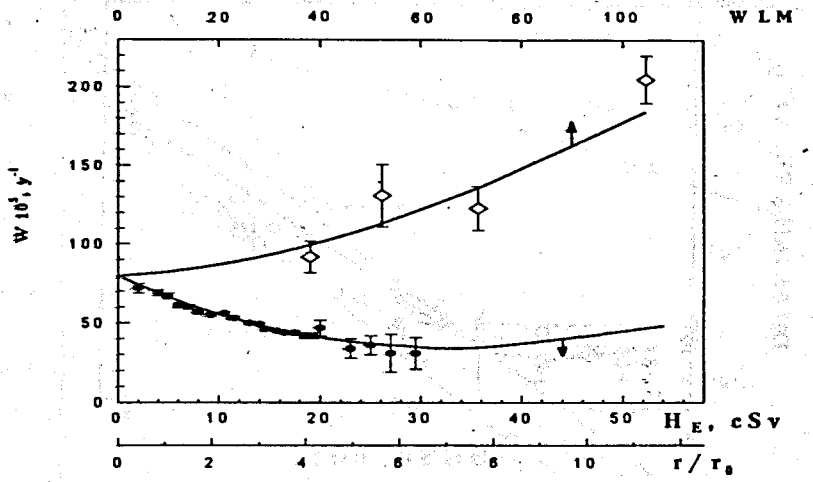

Fig.2. Lung cancer mortality W vs. radon level (r_0 — 37 Bq m^3; WLM — 0.5 cSv): •— in homes (Cohen B.L., 1995, from Ref.[13]); ◇ — in mines (ICRP, 1993, from Ref.[13]); ——— — fit to data of TDR model

are: $\mu_n = 0.66$ Sv^{-1}, $\mu_a = 1.022$ Sv^{-1}, $\nu = 0.95$ to solid cancer and $\mu_n = 0.4$ Sv^{-1}, $\mu_a = 0.16$ Sv^{-1}, $\nu = 1.02072$ to leukaemia. The significances W_c are assumed equal to 0.2 to solid cancer [20] and 0.0018 to leukaemia [18].

Figure 2 shows lung cancer mortality as function of radon level for two cohorts of human: the underground miners and the dwellers of the USA counties. An effective dose H_E of the dwellers is a cumulative dose over lifetime; an exposure of the miners at 1 WLM approximately creates the effective dose 0.5 cSv [13]. The TDR model results are calculated under the next conditions: $W = W/70$, where 70 is the lifetime significance, and W is calculated in accordance with (1) at $W_c = 0.0056$ [9,12,20]; the lower curve is calculated at $\mu_n = 1$ Sv^{-1}, $\mu_a = 0.5$ Sv^{-1}, $\nu = 1.22$, and the upper curve is calculated at $\mu_n = 1$ Sv^{-1}, $\mu_a = 0.644$ Sv^{-1}, $\nu = 0.98$. The significances of parameters reflect such a fact that the capability of the miners defence (immune) system is lower than the dwellers ones. Apparently it is connected with additional danger factors of miners. The epidemiological results of the lung cancer of Swedish dwellers without a hormesis are presented in [11].

4.2. Experimental Results with Mammalian Gells

Figure 3 presents the dicentric frequency in human lymphocytes as function of photon dose. The data points are displayed according to the experimental

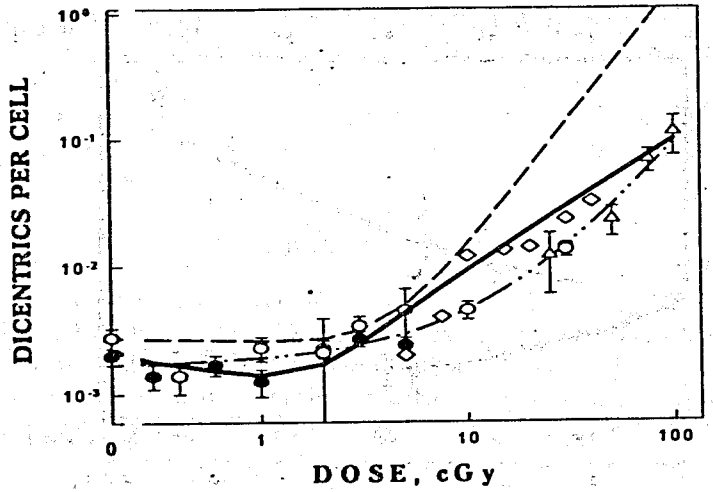

Fig.3. Dicentric yield as a function of a photon dose: ◇, ●, △, ○ — experimental results; ——— — fit to the data of TDR model; — · · , — — — — — fit to the data of linear-quadratic model

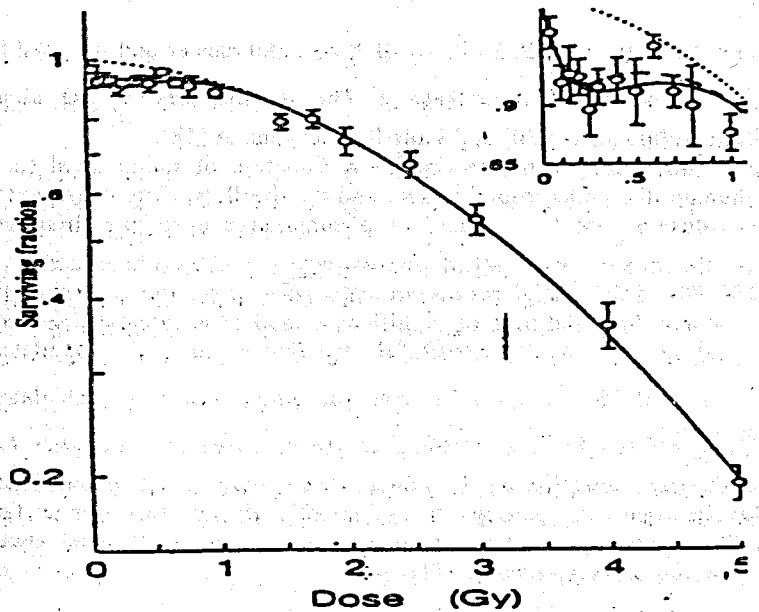

Fig.4. Survival of cell line HT29: data points are mean ± standard error; ····· — linear-quadratic model; ——— — induced repair model fit; - - - — TDR model fit

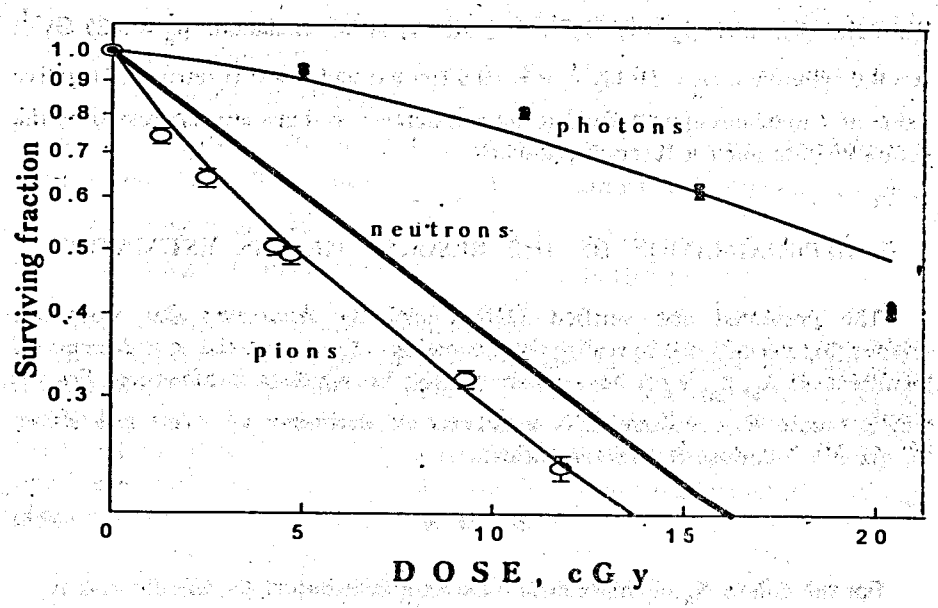

Fig.5. Survival of spermatogonia type B of mice after irradiation at peak dose in stooped negative pion, neutron and photon beams: data point — experiment, solid line — TDR model fit

results of the next studies [22—25]. The extremum of experimental results is described better by TDR model, as can be seen in Fig.3; the values of TDR model parameters calculated with formula (4) are: $\mu_n = 100\ \text{Gy}^{-1}$, $\mu_a = 0.1\ \text{Gy}^{-1}$, $\nu = 1.00193$.

Figure 4 shows the survival of human cell line HT29: the data points are experimental results [26], the curves — the fitting of defferent models to the data. The values of TDR model parameter fitting (formulas (7) and (10)) are: $\mu_n = 0.625\ \text{Gy}^{-1}$, $\mu_a = 0.606\ \text{Gy}^{-1}$; the values of ν are changed from 0 to 1.1 close for the dose of 0.15 in accordance to sigmoid shape of curve. It can mean the putting into operation of adaptive reaction close to dose 0.15 Gy^{-1}. Such phenomenon was observed earlier (see, for example, [27]). At the doses <1 Gy the linear-quadratic model substantially underpredicts the effect of *X* rays.

The survival spermatogonia type B of mice after exposure with different types of radiation [28] is shown in Fig.5. The mice were irradiated using Pu-Be neutrons, 14-MeV neutrons and high-energy neutrons up to 600-MeV (data points are not indicated in Fig.5). The parameter significances of TDR model fitting

(formula (9)) are: $\mu_n = 10\ Gy^{-1}$, for all types of radiation, $\mu_a = 6.25\ Gy^{-1}$, $\nu = 0.9$ (photons), $\mu_a = 50\ Gy^{-1}$, $\nu = -0.9$ (pions) and $\nu = 0$ (neutrons). Negative value of ν indicates apparently that the cell defence systems are suppressed by the action of pion nuclear reaction products.

5. APPROXIMATION OF THE RESULTS TO RISK ESTIMATION

The presented and verified TDR model for describing dose-stochastic relationship permits one to realize the estimations of radiation risk R at determined significances μ_n, μ_a, ν for human cohorts with known dose distributions. For the simplest case R is estimated as a product of derivative of effect probability W' (or $\Delta W'$) at dose H on its signification

$$R = W'H. \tag{15}$$

For the cohort N_0 of individuals with dose distribution dN/dH the risk is

$$R = \int_0^{H_m} W'H \frac{dN}{dH} dH, \tag{16}$$

where H_m is the maximum dose of the distribution. At low doses in accordance with (13) risk is a product of probability coefficient for stochastic effect (W') on H:

$$R = (1 - W_c)(1 - \nu)\mu_n H. \tag{17}$$

The application of the presented TDR model and formulas is illustrated by some examples.

5.1. Comparison of Probability Coefficient of Cancer Mortality W'_m

The most important result of epidemiological control of human exposure is the estimation of W'_m, which is based on extrapolation of risk from high to low doses studies. Such extrapolation on the base of TDR model formulas and the parameters of part 4.1 gives the following.

5.1.1. Comparison Results of W'_m on Base of Cancer Mortality of Japanese A-Bomb Survivors. The values of W'_m for lifetime risk are:

Solid cancer (without leukaemia)

— according with (14) at $W_c = 0.2$ $W' = 2.6 \cdot 10^{-2}\ Sv^{-1}$,

— according with ICRP [12] $W' = 4.5 \cdot 10^{-2}\ Sv^{-1}$.

All cancer

— according with (14) $W' = 1.8 \cdot 10^{-2}\ Sv^{-1}$,

— according with ICRP [12] $W' = 4.5 \cdot 10^{-2}\ Sv^{-1}$.

5.1.2. Comparison Results of W'_m on Base of Lung Cancer Mortality of Underground Miners. The values of W'_m without correction for lifetime risk are:

— according with (14) $W' = 1.9 \cdot 10^{-2}\ Sv^{-1}$,

— according with linear model $W' = 14 \cdot 10^{-2}\ Sv^{-1}$.

5.2. Estimation of Radiation Risk at JINR

The estimation of risk significance is calculated in accordance with (16). The dose distribution of the Joint Institute for Nuclear Research (JINR) staff is presented in [29] as typical for the last ten years. The relationship W' as function H is found on the base of (1), (9) and 5.1.1 for workers. The calculation result gives the next value of radiation risk level R of 2.500 workers of JINR using radiation sources:

$$R = \int_0^{H_m} W'H \frac{dN}{dH} = 0.1 \text{ cancer death/yr.}$$

This value is more than 30% as compared with a product of collective dose per year of JINR workers (5 Sv/yr) on W' calculated with (13). The risk calculation on base quantity W' recommended by ICRP [12] gives its value 0.2 cancer deat per year, that exceeds twice the risk value of TDR model.

REFERENCES

1. Zimmer R.G. — Studies on Quantitative Radiation Biology, Oliver and Boyd, Edinburg and London, 1961.
2. Timofeer-Resovski N.V., Korogodin V.I., Ivanov V.I. — Application of Hit Principle in Radiobiology. M.: Atomizdat, 1968 (Russ.).
3. Hug O., Keller A. — Stochastik der Strahlenwirkung. Sonderband zur Strahlentherapie. New York: Spinger-Verlag, 1966.
4. Kapultchevich V.G. — Quantitative Regularities of Ray Lesion of Cell. M.: Atomizdat, 1978 (Russ.).
5. Filushkin I.V., Perojan I.N. — Carcinogenic Risk Theory of Ionizing Radiation Influence. M.: Energoatomizdat, 1988 (Russ.).
6. Krasavin E.A. — RBE Problem and DNA Reparation. M.: Energoatomizdat, 1989 (Russ.).
7. Krasavin E.A., Kozubek S. — Mutagene Action of Radiation with Different LET. M.: Energoatomizdat, 1991 (Russ.).

8. United National Scientific Committee on the Effects of Atomic Radiation. 1986 report to the General Assembly, with annexes. «Genetic and Somatic Effects of Ionizing Radiation». New York, United Nation.
9. Komochkov M.M. — JINR, P16-96-70, Dubna, 1996.
10. Gofman J.W. — Chernobyl Accident: Radiation Consequences for This and Future Generations. Minsk: CNR Books and Vysshaya Shkola, 1994 (Russ.).
11. Luckey T.D. — Radiation Hormesis. Boca Ration, Florida, USA, CRC Press, 1991.
12. ICRP International Commission on Radiological Protection. 1990 Recommendation of the ICRP, Pub.60. Annals of the ICRP, 21, No1–3. Oxford: Pergamon Press, 1991.
13. Keirim-Markus I.B. — Atomic Energy, 1995, v.79, p.279.
14. Komochkov M.M. — JINR, P16-96-323, Dubna, 1996 (Russ.).
15. Geraskin S.A. — Radiation Biology. Radioecology, 1995, v.35, p.563 (Russ.).
16. Skov K.A. — Radiation Research, 1994, v.138, p.1.
17. Janeway C.A., Travers P. — Immunobiology. New York and London: Garland Publishing Inc., 1994.
18. Okada S. — JAERI-Conf. 95-010, Tokyo, 1995, p.5.
19. Kuzin A.M. — Ideas of Radiation Hormesis in Atomic Century. M.: Nauka, 1995 (Russ.).
20. Kellerer A.M. — Kerntechik, 1995, v.55, p.198.
21. Lagarde F. et al. — Health Physics, 1997, v.72, p.269.
22. Pohl-Ruling J. et al. — Mutation Research, 1983, v.110, p.71.
23. Lloyd D.C. et al. — Int. J. Radiat. Biol., 1992, v.61, p.335.
24. Luchnik N.V., Sevan'kaev A.V. — Mutation Research, 1976, v.36, p.363.
25. Sevan'kaev A.V. et al. — Radiation Biology. Radioecology, 1995, v.35, p.611.
26. Lambin P. et al. — Radiation Research, 1995, v.138, p.40.
27. Irushima T. — Proceedings of the Third Japan-US Workshop on Tritium Radiobiology and Health Physics, Nov. 8–10, 1988, Kyoto, Japan, 1989, p.189.
28. Baarly J., Bianchi M., Sallivan A.H., Di Paola M. — Proceedings of Symposium on Biological and Environmental Effects of Low-Level Radiation, Chicago, 3–7 November 1975, IAEA, Vienna, 1976, v.1, p.195; Komochkov M.M., Mokrov U.V. — JINR, P16-94-178, Dubna, 1994 (Russ.).

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