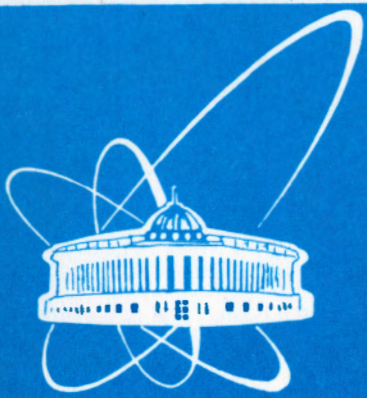

ОБЪЕДИНЕННЫЙ
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ИССЛЕДОВАНИЙ

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M.M.Komochkov

DOSE DEPENDENCE ON STOCHASTIC RADIOBIOLOGICAL EFFECT IN RADIATION RISK ESTIMATION

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Комочков М.М.
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Зависимость стохастического радиобиологического эффекта от дозы при оценке радиационного риска

Выполнен анализ результатов наблюдений взаимосвязи доза — эффект на клеточном и организменном уровнях с целью уточнения коэффициентов риска при малых дозах. Результаты наблюдения представлены двумя противоположными группами зависимостей эффекта от дозы: надлинейной и подлинейной. Оба типа зависимостей описываются решениями уравнения предполагаемого единого защитного механизма из двух составляющих: врожденной (конститутивной) и адаптивной или индуцибельной. Анализ последних данных по надлинейным зависимостям показывает значительную недооценку по сравнению с рекомендациями МКРЗ радиационного риска всех видов рака, кроме лейкемии, для некоторых критических групп из популяции, при малых дозах облучения. С ростом дозы наблюдается снижение величины эффекта на единицу дозы, что, возможно, связано с включением активности адаптивного защитного механизма при превышении некоторых пороговых значений дозы.

Работа выполнена в Отделении радиационных и радиобиологических исследований ОИЯИ.

Препринт Объединенного института ядерных исследований. Дубна, 1999

Komochkov M.M.
E19-99-295

Dose Dependence on Stochastic Radiobiological Effect in Radiation Risk Estimation

The analysis of the results in dose — effect relationship observation has been carried out on the cell and organism level, with the aim to obtain more precise data on the risk coefficient at low doses. The results are represented by two contrasting groups of dose dependence on effect: a downwards concave and a J-shaped curve. Both types of dependence are described by the equation solutions of an assumed unified protective mechanism, which comprises two components: constitutive and adaptive or inducible ones. The latest data analysis of the downwards concave dependence curves shows a considerable underestimation of radiation risk in all types of cancer, except leuceumia, for a number of critical groups in a population, at low doses comparing to the ICRP recommendations. With the dose increase, the decrease of the effect value per dose unit is observed. It may be possibly related to the switching of the activity of the adaptive protective mechanism, with some threshold dose values being exceeded.

The investigation has been performed at the Division of Radiation and Radiobiological Research, JINR.

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1. INTRODUCTION

One of the main purposes of radiological protection is the determination of the radiation risk (RR) level. RR evaluations are committed generally to control health effects of exposure and to establish exposure limits. The formalized basis of these activities are the safety standards, as well as recommendations of the International Commission on Radiological Protection (ICRP). According to these documents to evaluate the risk W, irrelevant to the dose, it is necessary only to multiply two values: the ionizing radiation dose H and the risk coefficient W', the values of the latter tabulated [1]. The main merits of this linear no-threshold (LNT) hypothesis are its simplicity and ability to be used for the collective dose. But numerous facts, however, contradict the LNT hypothesis (as in [2-7], for example). The most striking example of the controversy are two mutually excluding predictions for humans, exposed to irradiation after the Chernobyl accident [8,9]. J.W.Gofman predicts that " ... the accident at the Chernobyl Nuclear Power Station (ChNPS) will cause 300.000 lethal outcomes from malignant tumours..." [8]; T.D.Luckey informs on a 20.000 prevention of lethal outcomes from cancer in republics, subjected to the aftermath of the ChNPS accident. This contradiction is the result of the authors' attempts to rely on different dose – effect relationship for the same radiation environment and conditions. The contradiction will grow into a grave problem if we take into our consideration the fact that the LNT hypothesis critics separated into two confronting groups. Members of the first one support views, which are partially close to Gofman's, members of the second hold the views of Luckey. Schematic dose-effect relationship in representation of the two groups G (downwards concave curve) and L (J-shaped curve) are shown in Fig.1. The given data show a kind of uncertainty area. Inside this area, straight lines show the dose-effect relationship, which are the basis for the ICRP Recommendations in Publications 26 [10] and 60 [1]. All the presented dependence lines must intersect in the area of epidemiological data, which are, principally, their basis. The epidemiological data basis is formed by the results of the survey of a cohort of Japanese survivors after atomic bombardment. These data, taken as a basis of the ICRP Recommendations [1], are in the interval of 0.2 to 3 Sv. At doses less than 0.2 Sv there is the extrapolation zone which goes to 10-5 Sv - the negligible individual dose admitted in the USA [11]. Thus, the extrapolation zone covers four orders,

in dose values as well as in effect values, if the LNT dependence is accounted for in the last case. Concerning radiation situation and irradiation impacts almost all population of the Earth is covered by the extrapolation zone. In this aspect, the high significance of extrapolation models for epidemiological data in low dose studies becomes obvious.

The given paper, on the basis of the Two Protective Mechanisms (TPM) model [12], analysis the results of the recent years' studies which present examples of the dose – effect relationship of G- and L-type (Fig.1). Evaluations of risk coefficients for the dose – effect relationship of G-type are made on the basis of the analysis, and they are compared to the analogeous ones, obtained with the LNT dependence.

2.DOSE – EFFECT RELATIONSHIP, TYPE L.

On the cell level, the example of the L-relationship is the data from papers [13, 14]. They are shown in Fig.2 together with the results of their analysis on the basis of the TPM model [12]. According to this model the effect (i.e. the dicentrics' yield) is presented by two components:

$$W = W_n - W_a , \qquad (1)$$

where W_n is the dicentrics' yield (the formation probability) in the absence of effective adaptive or inducible repair, W_a - the successful adaptive or inducible repair yield, W - the resulting yield of dicentrics. The TPM model allows to present the formulae for W_n and W_a in the following way:

$$W_n=1-(1-W_c)\exp(-\mu_n D) , \qquad (2)$$

$$W_a=[(1-W_c)\,\nu\mu_n/(\mu_n-\mu_a)][\exp(-\mu_a D)-\exp(-\mu_n D)]. \qquad (3)$$

Here μ_n is the constituent or innate radiosensitivity (alteration of the number of cells which escaped the primary damage effect, per one and the same such cell and per dose unit), μ_a - adaptive or inducible radiosensitivity (alteration of the number of cells which escaped the effect due to the action of the adaptive or inducible protective mechanism, per one cell and per dose unit), ν is the average number of induced repair per one primary lesion (the coefficient of capabilities of the adaptive protective mechanism [12]), W_c is the effect probability (i.e. dicentric yield) in the control. Under the concept of the primary damage any damage is ment, which lead or could lead (in case of no adaptive or inducible repair) to the discussed effect (dicentric). The dependence of the primary damage

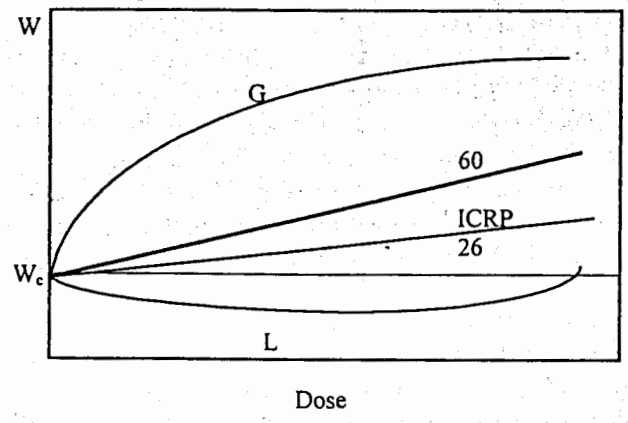

Fig.1 Dose – effect (W) relationship in different presentations, W_c - spontaneous effect (background).

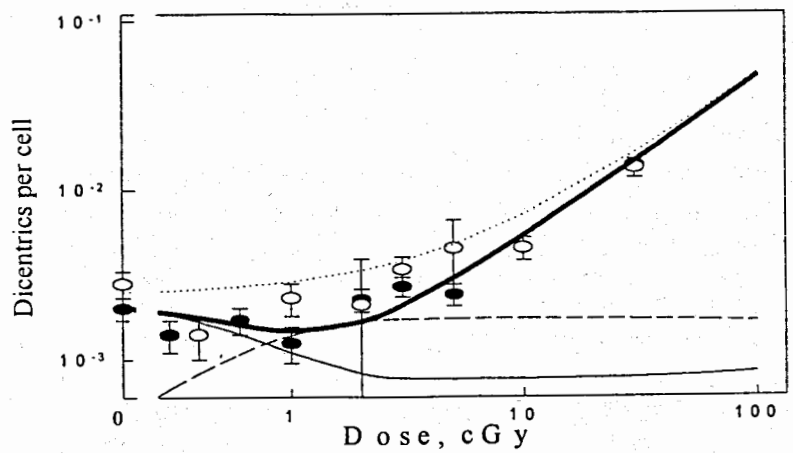

Fig.2 Analysis of the dicentric yield dependence in the lymphocyte culture on the dose of X-ray radiation on the basis of TPM model:
W_n is the yield (formation probability) of dicentrics, with no account to the adaptive or inducible repair, W_a is the yield of adaptive or inducible repair,
W is the resulting yield of dicentrics.

on the dose is represented in formula (2), in Fig.2 it is shown with a dotted line. The broken line is described with formula (3) and shows the yield of adaptively or inducibly, successfully reparated cells. The first component in (3) represents the yield of all adaptive or inducible repair, the second - unsuccessful repair (miss-repair). The full line shows the resulting yield of dicentrics (W). The μ_n, μ_a, ν obtained by the best agreement method of the calculated and measured values of the dicentric yield, comprise relatively, 0.00047 cGy^{-1}, 1.62 cGy^{-1} and 5.97. The analysis of formula (3) shows a maximum in the dependence of W_a on D. The D_m dose, when the W_a maximum is observed, can be obtained with (4):

$$D_m=\ln(\mu_a/\mu_n)/(\mu_a-\mu_n). \quad (4)$$

In our case the value of D_m is approximately equal to 5 cGy.

The effect value per dose unit or risk coefficient [1] is described by the derivative W on the dose, which, at low doses ($\mu D << 1$), takes the following form [12]:

$$W' = (1-W_c)(1-\nu)\mu_n. \quad (5)$$

Inserting the observed (Wc) and the obtained values μ_n, ν into (5), we receive the risk coefficient of -0.2 Gy^{-1}. Minus before the figure means a decrease in the dicentric yield with the dose growth.

Thus, the linear dose – effect relationship may be accepted on the cell level of the induction effects of the X-ray radiation with the dicentric formation in the lymphocyte culture only at doses much lower than 1 cSv and with the decrease of the effect, while the dose rises, due to the yield in the control. It is caused by the activation of the adaptive protective mechanism, which makes the basis of the TPM model [12]. It is proved in paper [7] in the form of "activation of the damage control".

On the *level of human organism* two papers - [15], [16] - may be regarded as examples of L-relationship. The papers present one type of the effect, lung cancer, as a result of the ionizing radiation exposure. On the basis of the TPM model we analyze results [16], as the analysis of results [15] is presented in paper [12]. The epidemiological survey data [16] are given in Fig.3 by the dose dependence on the disease and/or on the lung cancer death *RR* resulting from an exposure to X-rays in radiotherapy and fluoroscopy. The analysis of the observed results was performed with the following formula:

$$RR = W/W_c = (W_n - W_a)/W_c = RR_n - RR_a, \quad (6)$$

where RR_n is the relative risk under the condition of only the innate protective mechanism (innate immunity, [17]), RR_n is the relative risk prevented by the action of the adaptive protective mechanism (adaptive immunity, [17]). The components of the RR_n and RR_a relative risk are described with (2), (3) and (6) at the following value definitions: μ_n - the innate radiosensitivity (the alteration of the number of people who avoided cancer formation due to the innate protective mechanism only, per person and per dose unit), μ_a - the adaptive radiosensitivity (the alteration of the number of people who avoided cancer formation due to the adaptive protective mechanism action, per person and per dose unit), ν - the coefficient of capabilities of the adaptive protective mechanism(mean number of people who are capable to avoid cancer due to the action of the adaptive protective mechanism or the adaptive immunity, per one cancer nidus, with the action of the innate protective mechanism only). The control effect or the probability of spontaneous cancer diseases and/or deaths (Wc) is adopted 0.03, according to the data, presented in paper [3]. The analysis results are given in Fig.3. The values μ_n, μ_a, ν are obtained from the best agreement condition of calculation of the observed results and estimated ones. Assumptions a priori were used concerning the value μ_n, which was chosen close to the radiosensitivity value for miners, whose adaptive protective mechanism is mainly depressed [12]. The obtained values comprised $\mu_n = 0.02$ Gy^{-1}, $\mu_a = 0.59$ Gy^{-1}, $\nu = 1.87$, $W' = -0.017$ Gy^{-1}, $D_m = 5.9$ Gy.

Summarizing, we state that the analysis of the discussed formulae and results allows to assume that the L-type of the dose – effect relationship takes place at $\nu>1$, i.e. when the active ability resource of the adaptive protective mechanism is sufficient not only for the damage elimination after ionizing irradiation, but for the removal of a part of spontaneous damage. It is observed in the region of low doses. However, with the increase of the dose and the amount of the adaptive radiation-induced damage, the relative yield of the adaptive protective mechanism in damage removal grows lower and lower. The decrease in the activity of the adaptive protective mechanism can be the cause of it, after passing the maximum at D_m. The dose-effect relationship of the similar quality is presented in paper [7]. The model, suggested by the authors of [7], like the TPM model, is a resulting effect of two components, one of which (adaptive) is described by two terms. The similiarity of the dose – effect relationship analysis, type L, in the present paper and in paper [7], testifies the efficiency of the TPM model.

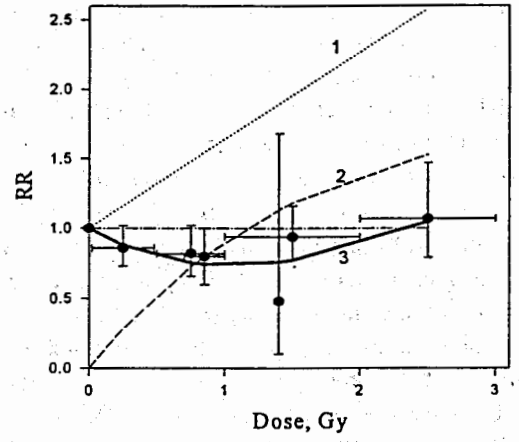

Fig.3 Relative risk (RR) of disease and/or death from lung cancer as a result of human exposure toX-rays or gamma-radiation:
1 - RR in the condition of innate protective mechanism only,
2 - prevented RR due to adaptive protective mechanism,
3 - resulting RR and the observation results (•[17]).

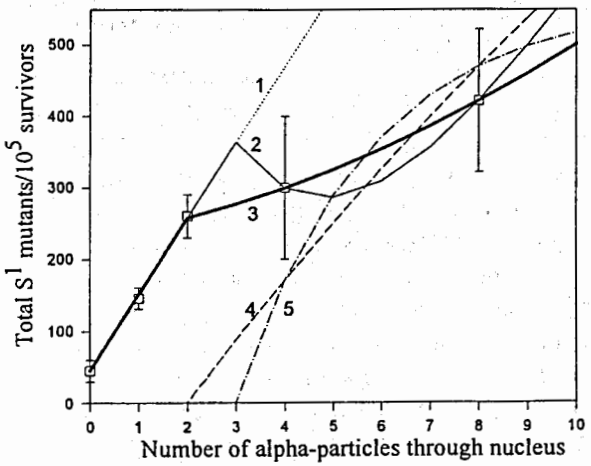

Fig.4 The yield of S1 mutations per 100,000 survived mammalian cells at their irradiation with alpha particles 90 keV/μm (•[18]); two variants of the analysis are presented: the first one - inducible repair starts acting at two α-particles through a nucleus (1 - mutation yield in the absence of inducible repair - W_n, 4 - prevented by inducible repair mutation yield - W_a, 3 - resulting mutation yield - W), the second one - inducible repair starts acting at three α-particles through a nucleus (1 - W_n, 5 - W_a, 2 - W).

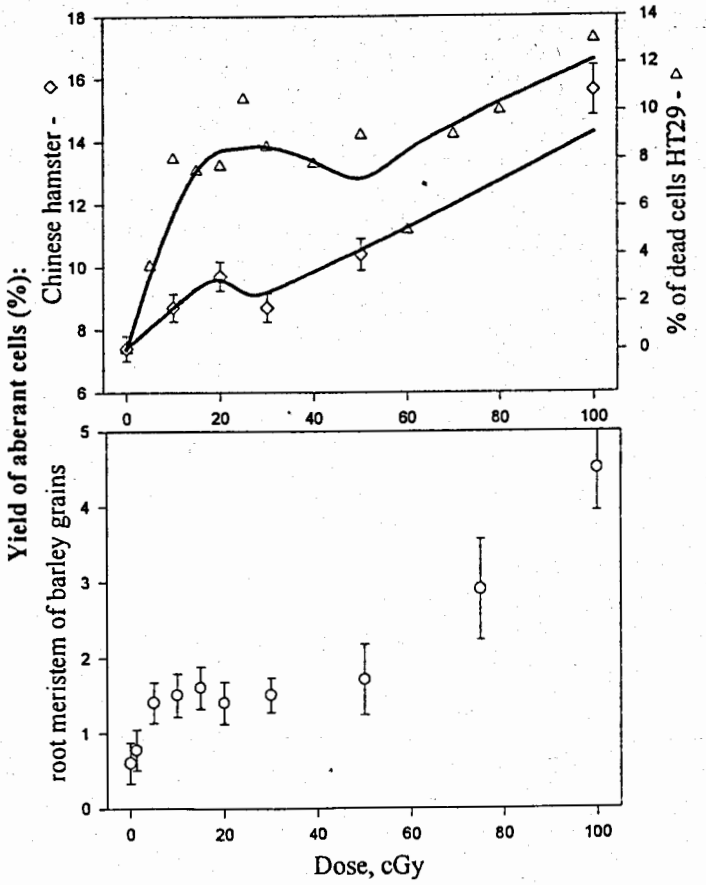

Fig.5 Dose – effect relationship in cells of different biological objects: HT29 human lines, V79 Chinese hamster lines and root meristem of barley grains - fitting results by the TPM observation data.

3. DOSE – EFFECT RELATIONSHIP, TYPE G

On the cell level G - relationship may be represented by the data from papers [18-21], together with the analysis results (Fig.4) and fitting (Fig.5). The data analysis of paper [18] is conducted with formulae (1)-(3). There, W is the yield of mutations, D is α-particle number through a nucleus, μ_n and μ_a are radiosensitivity, constitutive and inducible, respectfully, α-particles through a nucleus^{-1} (α^{-1}). It was supposed during the analysis that the adaptive or inducible protective mechanism set out acting with two α-particles through a cell nucleus (the first variant) or with three α-particles (the second variant). The analysis resulted in the following values:

in the first variant - $\mu_n = 0.00106\ \alpha^{-1}$, $\mu_a = 0.0408\ \alpha^{-1}$, $\nu = 0.83$,

in the second variant - $\mu_n = 0.00106\ \alpha^{-1}$, $\mu_a = 0.357\ \alpha^{-1}$, $\nu = 1.9$.

The variant analysis results differ considerably, but in both cases a decrease is observed in the effect per α-particle (dose unit) after 2-3 α-particles through the nucleus, which is characteristic of the G- relationship. The percentage of dead cells of the HT29 line of human tumour is determined as the diversity between the initial percentage of cells (100%) and the survived cells' percent, measured in paper [19]. The data for the cell V79 line of the Chinese hamster are taken from paper [20], for the cells of barley root meristem - from paper [21]. The effect alteration per dose unit in the interval of 5-50 cGy or 2-3 α-particles in the frames of the TPM model is interpreted as the beginning of the action of the adaptive or inducible protective mechanism.

On the organism level the G-type dose – effect relationship is presented by the data from papers [22, 23], shown in Fig.6 together with the results of the analysis at doses lower than 40 cSv (weighted colon dose *H*). The analysis was done with (7).

$$ERR = RR - 1 = (1-W_c)(1-f)/W_c, \qquad (7)$$

where ERR is the excess of the relative risk; RR is the relative risk, and f is determined in [12] with formula (8) for the case of the adaptive protective mechanism on several levels (cell, tissue, organism):

$$f = \exp\left(-\mu_n H\right) + \sum_{i=0}^{i=m} \frac{\nu_i \mu_n}{\mu_n - \mu_{ai}} \left\{\exp\left[-\mu_{ai}\left(H - H_i\right)\right] - \exp\left[-\mu_n\left(H - H_i\right)\right]\right\} \qquad (8)$$

at $(H-H_i) \geq 0$ *and* $H_0 = 0$.

In accordance with the foundations of the TPM model, μ_n is accepted constant in relation to the *H* dose, the adaptive radiosensitivity μ_{ai} and the coefficient of

capabilities of the adaptive protective mechanism ν_i are presented changing discretely on the boarders of the dose region *i* and *i+1*; and they remain constant in the interval between the boarders. The regions' boarders may be interpreted as a recurrent level of the adaptive protective mechanism (the cell level, the tissue level, the organism level), which starts acting at the dose H_i. The line on Fig.6 is the results of the observed data fitting with formula (8) at m=1 and H_i=3.8 cSv. The analysis was not conducted as there could be a possible influence in the result inhomogeneity of a Japanese cohort on the innate radiosensitivity. Fig.7 is the extension of Fig.6 into the high dose region. The data presented there, are borrowed from paper [23] for the dose intervals bigger than those in paper [22]. The values μ_n, μ_{ai} and ν_i are found from the best agreement condition of the calculated and measured values (Fig.6, 7); the effect probability in the W_c control (background risk) is assumed to be equal to 0.28 death from solid cancer [23].

The excess of the absolute risk (EAR) of death from leukemia among Japanese of both sexes and all ages is presented in Fig.8. Also, there are the fitting results of the observed data with the following formula of the TPM model:

$$EAR = (1-W_c)(1-f). \qquad (9)$$

The background risk from leukemia (W_c) is assumed to be equal to 0.006 on data base [23].

Death probability (W) per dose unit (W') or the risk coefficient can be obtained with the following formulae:

$$W' = (EAR)' = W_c(ERR)'. \qquad (10)$$

The results of the W' determination at the dose, going to "0", are shown in the table; in the same table, for comparison, the values of W' from other papers are given. It may be concluded from the table that the values of the risk coefficient change more than one order, depending on the method of determination, dose range and the initial information. The ICRP Recommendations are not considered to be the evaluations overestimating the risk, as some specialists think [2-4]. The risk coefficient determination at low doses with results' extrapolation to high doses, as ICRP recommend [1], may lead to grave errors.

4. CONCLUSIONS

Nowadays, we have to admit that the forecast of consequences of exposing humans to radiation, especially at low doses, tends to a great extend of uncertainty. It is testified by the facts as well as by the model estimations. In human population exposed to radiation, there is always a group, whose health

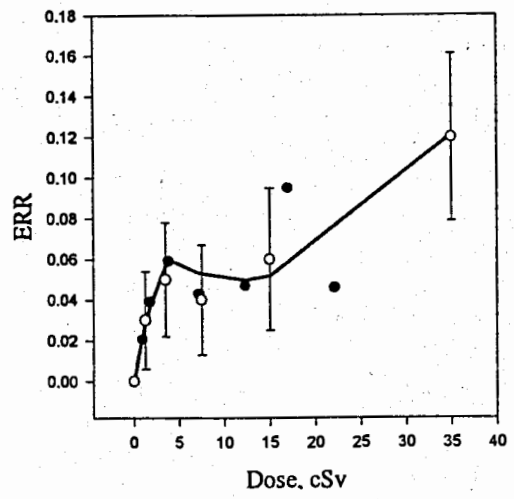

Fig.6 Excess of the relative risk (ERR) of death from all types of cancer except leukemia among the inhabitants of Hiroshima and Nagasaki, subjected to the atomic bombardment at the age of 30:
•, o - the results of epidemiological surveillance with definition into small (at low doses [22]) and large intervals [23], respectfully,
—- - results of the TPM model fitting.

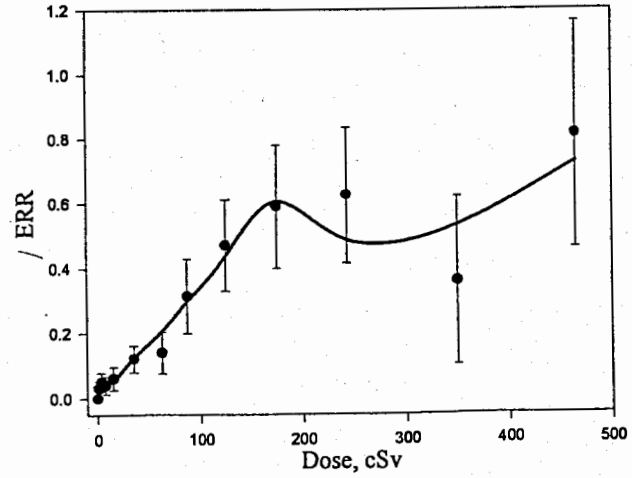

Fig.7 Excess of the relative risk (ERR) of death from all types of cancer except leukemia among the inhabitants of Hiroshima and Nagasaki, subjected to the atomic bombardment at the age of 30:
• - epidemiological surveillance results [23], —- - TPM fitting results.

Risk coefficients, death from cancer W'
(different data and determination methods)

$W' \cdot 10^2$ Sv^{-1}	Cancer type	Category of exposed humans	Determination methods	Year, references
1.2 - 11 5 0.12 - 2.5	all all leukemia	all	linear no-thres-hold model (LNTM)	1972 - 1990 1990, ICRP 1972-1990; [1]
0.07	leukemia	Japanese, age 30	at dose 10 cSv	1996[9]
10	solid	Japanese men age 30	LNTM at dose < 300 cSv	1996 [9]
10	solid	Japanese men age 30	LNTM at dose < 50 cSv	present paper*
45	solid	Japanese men age 30	LNTM at dose < 5 cSv	present paper*
56	solid	Japanese men age 30	TPM model, LSM** at dose going to 0	present paper on data base [8]
-0.02	leukemia	Japanese	TPM model, LSM** at dose going to 0	present paper on data base [8]

*) The W' value is obtained as a multiplication of death probability from spontaneous cancer during life-time (0.28) by the value of the relative risk excess of death from cancer in Japanese men, who were 30 years old at the time of bombardment, per 1Sv [8].
**) LSM -the least square method.

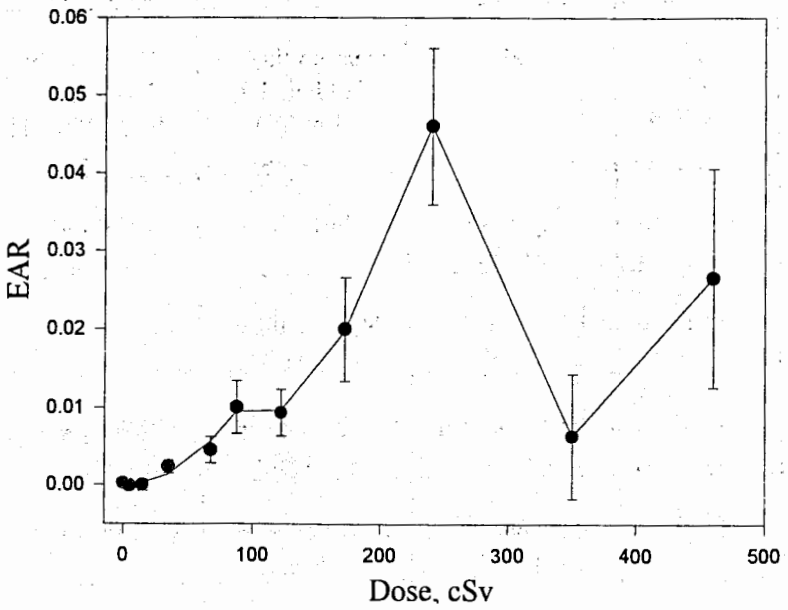

Fig.8 Excess of the absolute risk (EAR) of death from leukemia among the inhabitants of Hiroshima and Nagasaki during the observation period, from 1950 till 1990: • - epidemiological surveillance results,
— - TPM fitting results.

damage must be evaluated with maximum risk values, which are much higher than those recommended by ICRP. At the same time, in the human population exposed to radiation there can be found a group, to whom the risk is negligible, it can even take negative values, like in the exposure at doses on the professional workers level. The ICRP recommendations cannot be considered the upper overestimated evaluation of the risk, as many specialists believe. One of the conditions to increase the trustworthiness of radiation risk evaluation is the necessary information about people radiosensitivity and their protective system reserves.

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