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United States-Russian Workshop on the Stochastic Health Effects of Radiation

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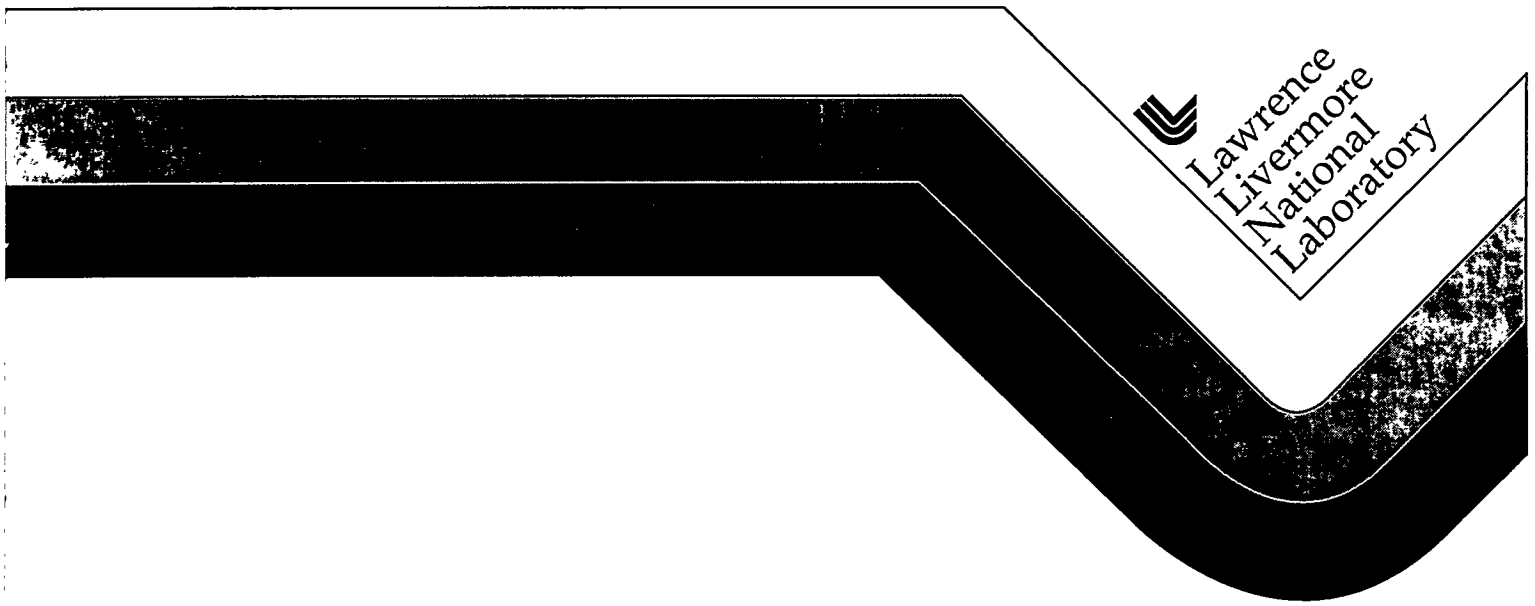

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United States-Russian

Workshop on the

Stochastic Health Effects of Radiation

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Land, C.E.	*Radiation dose, Reproductive History, and Breast Cancer Risk Among Japanese A-Bomb Survivors*
Catlin, R.J.	*Analysis of the Pace University Center for Environmental Legal Studies Report of September 1990 Entitled "Environmental costs of Electricity" by R.L. Ottinger, D.R. Woolley, N.A. Robinson, D.R. Hodas, and S.E.Babb.*

Conclusions

This Report is Dedicated to the Memory of Dr. Edward Shoemaker

As a major force in the International Cooperative efforts of the U.S. Nuclear Regulatory Commission, Dr. Shoemaker worked tirelessly with the scientists participating in this workshop. His enthusiasm and competence, his humanity and sensitivity, all contributed to making this workshop effective, significant and a first step to the beginning of a long term collaborative research program between our two countries.

WE SHALL NOT FORGET HIM

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FORWARD

In August 1988, two years after the Chernobyl accident, the United States and the Soviet Union signed an agreement to sponsor a Joint Coordinating Committee on Civilian Nuclear Reactor Safety, (JCCCNRS). A range of tasks were to be performed, including one on Environmental Transport (7.1) and on Health Effects (7.2). In Working Group 7.2, there were several tasks, one of which was to sponsor a workshop on the stochastic effects of radiation.

The Soviet Union agreed to provide some information on late effects of radiation exposures and to attempt to add some new insights into low dose and low dose rate radiation consequences. At that time, it had just been revealed that significant radiation exposures had occurred in the South Ural Mountains, associated with the early years of operation of the MAYAK nuclear complex.

The need to be able to better predict the long term consequences of overexposures, such as occurred with the Chernobyl accident, was a major factor in organizing this workshop. We decided to invite a small number of experts from the Soviet Union, who had direct knowledge of the situation. A small group of American experts was invited to help in a discussion of the state of knowledge of continual low level exposure. The experts and expertise included:

aspects of basic theoretical rabiobiological models,
studies on experimental animals exposed to chronic or fractionated external or internal radiation,
studies on populations exposed to chronic intake and continual exposures,
workers exposed to low or high continual levels of radiation.

The intent was to begin a dialog on the issue of a better understanding of the dose rate effect in humans. No detailed conclusions could be reached at this first interaction between out two countries, but a model was prepared which seems to support a range of what are known as low dose and dose rate effectiveness factors. A beginning of an evaluation of the role of radiation dose rate on leukemia risk was also accomplished.

There was no requirement to prepare formal papers, and some of the Americans brought reprints of earlier publications, or figures from their published work. Because there was little knowledge of the Soviet experience and data, we asked our Russian visitors to prepare informal briefing papers to assist in understanding their experience. We have included all of their papers as well as a few of the American papers which had been prepared for this Workshop. We spent much of the final hours preparing an executive summary as a distillation of our efforts.

The Soviet team was led by Dr. Igor Filyushkin, and Professor Marvin Goldman led the American side. Drs. Ginevan, Shomaker and Yaniv not only represented their sponsoring agencies, but actively participated in all aspects of

the meeting. The co-chairs gratefully thank the sponsors and the scientists and their staff for their dedication and assistance in making this a most interesting, challenging and thought provoking interaction. In the years that have followed, the interactions that began at Davis have expanded, and a new, longer-term research collaboration is beginning which will continue the work begun at this meeting.

for the Russian side

Igor Filyushkin

for the American side

Marvin Goldman

Davis, California
December 1994

Attendees

RUSSIA

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I.M. Petojan, Moscow, Ministry of Health, Biophysics Institute
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Technical Assistance

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Executive Summary

This report addressesone of the tasks agreed upon in the area of Environmental Transport and Health Effects (Working Group 7.2) of the JCCCNRS, i.e. to hold a workshop on the topic of the role of radiation dose rate effects on stochastic risks for low LET radiation.

The Chernobyl Nuclear Power Plant accident in April 1986, released a very large quantity of radionuclides, and the populations, were exposed primarily to low LET radiation, from ^{131}I, ^{134}, ^{137}Cs and ^{90}Sr. Carcinogenic risk resulting from low level/low LET radiation exposure, has never been observed. There is very little epidemiological information on the risks to population from low level radiation exposure. Our major data base, which strongly influences all international and national quantitation of radiation risk, is derived from the study of the survivors of the atomic bombing of Hiroshima and Nagasaki, a situation in which the dose was delivered instantaneously and the dose rate was essentially infinite. Other widely known human studies are generally to fractionated high dose rate exposures or to continual exposure to high LET radionuclides.

Problems of extrapolation of data derived from long term, low LET radiation exposure of experimental animals is hampered by the lack of verified scaling factors for time, for pathology and physiology differences and for cancer sensitivity of specific tissues.

While the weight of fragmentary evidence supports the use of a low LET dose rate effectiveness factor of about 2-10 or more, there are few "solid" data in human experiences to confirm the appropriate value. In attempting to anticipate and perhaps forecast potential consequences to Chernobyl exposed populations, this workshop was developed as a first step in reducing the uncertainty about the dimensions of low dose rate effectiveness in induction of stochastic health effects. Newer knowledge of fundamental processes, additional insights into radiation carcinogenesis and the recent availability of new information on Russian populations exposed in the South Urals, provide an opportunity to address this issue. A unique feature of the post Chernobyl accident situation is the presence of internal and external exposures and the non uniformity of tissue absorbed radiation doses.

No information has been published on effects of mixed radiation exposures, and the usual practice has been to determine these independently and add them.

In the recently revealed information on populations in the Urals, who received their exposures primarily some 35 to more than 40 years ago, we have an opportunity to learn more about the role of low dose rate exposures to internal and external low LET radiations. The available information is considered preliminary. Problems in retrospective dosimetry and in epidemiological follow-up have yet to be solved.

The workshop provided an opportunity for radiobiologists and epidemiologists to review and discuss the epidemiological data, the lessons from laboratory studies and reach conclusions on low level risk assessment resulting from the fundamental knowledge and theoretical models.

Brief presentations were made by the attendees, and these are summarized herein. In addition many of the attendees prepared manuscripts which are included in this report.

The discussion centered on a set of questions and insights in to three general areas of low radiation dose rate science: epidemiological, experimental and theoretical.

Epidemiological questions and needs were also discussed. When do exposed people show their cancer effects? With protracted exposure the concept of "latency" is obscured since the exposure time is long. The time of first recognition of the stochastic effect and the time of exposure onset are at least two of the temporal factors. For the exposed Russian populations, (Chernobyl and South Urals [and perhaps others]), comparison of appearance times of cancers with those from the Japanese data base can be used in an attempt to develop a time and age specific "incidence rate." Particular cognizance should be paid to the fact that some stochastic effects (cancers) are not immediately apparent or life threatening.

Dose rate effects revealed in epidemiological observations may be influenced or altered by factors other than radiological. Those should include accounting for the possible role of sex, age at exposure, other environmental or occupational exposures, "cultural" and dietary influences, and the presence of possibly different genetic subgroups; e.g. Russian vs. Tartar.

The summaries of the South Urals data were compared with those from the United Nations reports, the U.S. National Academy of Sciences reports, the ongoing occupational studies in the U.S. and some of the animal fundamental and theoretical studies. Some of these are shown in the table.

TABLE
"STUDIES OF POPULATIONS RECEIVING DIFFERENT DOSE RATES"

An attempt at developing a unifying "schema" on dose rate effectiveness is shown in the figure. The Japanese a-bomb data base, the "ultimate high dose rate," was assigned a value of unity.

FIGURE
"DOSE RATE EFFECTIVENESS FACTORS"

In considering the dose rate of protracted exposure, the conventional use of total dose or average annual or quarterly dose were considered inadequate. It is necessary to also include some information on the temporal distribution of dose. Since no single parameter seems adequate, a preliminary specification should at least consider the magnitude and duration of peak dose rate. In reality, there is no universal symmetrical temporal model that is acceptable. Perhaps a dose-time product concept incorporating a "full width at half height" of the peak can be helpful. Our focus was on how the cells at risk "saw" the incident fluence of radiation.

In answering the question about whether we can obtain individual dose estimates, the temporal distribution of dose is but one consideration. The data must provide the temporal aspects of both internal and external dose so as to permit a credible estimate of individual organ doses. A technique in which the risk of cancers in individual organs is summed to derive the overall risk has been proposed. In derivation of risk factors for specific organs different models might be used for different organs (e.g. relative or absolute temporal risk projection models). Such an integrated model, which is normalized with regard to organ absorbed doses and "weighted" by organ specific risks coefficients can be an important step in understanding of overall risk .

Tentative conclusions which were developed at the meeting are:

1- Low LET exposures at low doses and/or rates are obviously less effective at producing stochastic health effects than are high, acute doses.

2- For the epidemiological studies for which such dose rate data exist, the lower the dose rate, the greater the apparent amount of reduction of consequences.

3- For radiation-induced leukemias, peak dose rates of about 10^{-5} Gy/da have not been associated with an increased risk in US nuclear workers.

4- Preliminary evaluation of a cohort of Russian nuclear workers exposed to peak dose rates of about 10^{-1} Gy/da showed an increased risk which was between 20 to 80 % of the risk seen in atomic bomb survivors.

5- Thirty to 70% reduction in comparable risk was seen in populations exposed to radionuclide releases, (10^{-4} to 10^{-2} Gy/da peaks), near the Tech River in Russia some 40 years ago.

6- Radiation therapy cohorts have also demonstrated a reduction in risk.

7- Further follow-up of exposed populations is needed as is a more intensive program of retrospective dosimetry.

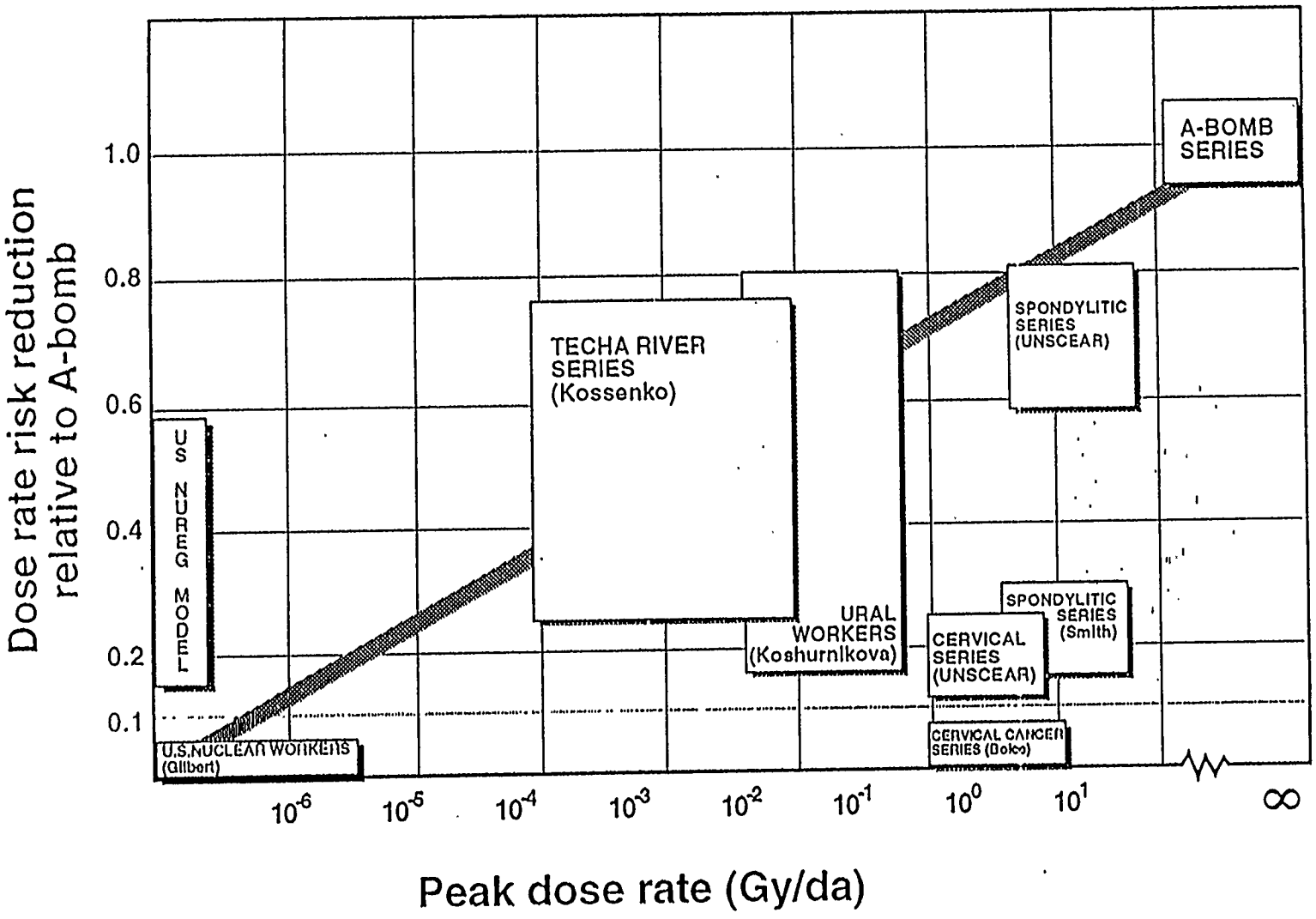
8- Other cancers may provide similar dose rate relationships. The radium dial luminizer population may be an example of dose rate effectiveness associated with high LET exposures.

Table 1 - Human Radiation Leukemia * and "Peak" Dose Rates

Author	Series	Gy/da	Plateau Risk per P*Y*Gy
UNSCEAR 88	A bomb	∞	2.94 x 10 -4
	spondylitis	~1	2.02 x 10 -4
	cervical	0.1-1	0.61 x 10 -4
Smith 82	spondylitis	~1	0.54 x 10 -4
Boice 88	cervical	0.01-1	0.1 x 10 -4
Koshurnikova 92**	Ural workers	~ 0.01	0.6 - 2.3 x 10 -4
Kossenko 92**	Techa River series	~ 0.001	~ 0.7 - 2 x 10 -4
Gilbert 91	US nuclear workers	< 0.00001	~ 0.0 x 10 -4

*Modified from Filyushkin, **Preliminary estimate

Figure 1 - Radiation Leukemia Series



THEORY OF THE INDUCTION OF BONE SARCOMA BY BONE-SEEKING ALPHA EMITTERS AND ITS APPLICATION TO RISK ASSESSMENT

I.M. Petojan

ABSTRACT

This work discusses the theory of bone sarcoma induction by bone-seeking alpha emitters, which is based strictly on biological considerations relative to the mechanism of radiation-induced carcinogenesis, identification of cells at risk and their location in bone, bone tissue renewal processes and bone cell kinetics with or without radiation exposure. The model is consistent with the data on bone sarcoma incidence humans with incorporated long-lived isotopes Ra-226 + Ra-228. Extrapolation of these data to a low-intake region on the basis of the developed theoretical approach suggests that the linear ICRP-UNSCEAR model overestimates carcinogenic risk at low doses, possibly by a factor of 2-4. The model suggests a linear response of target cells to the initiation effects of alpha irradiation. The non-linear (linear-quadratic) initial part of dose-response curve for osteosarcoma induction is explained quantitatively by a model based on a promoter effect of regenerative hyperplasia resulting from inactivation effects of alpha radiation. The maximum overestimation inherent to the model of the low-level risk due to dose-dependent promotion factor is estimated using bo^{+1}/bo, where bo is a model parameter which is proportional to the normal division rate of osteogenic cells in vivo and which can be estimated within the framework of the model. The model provides confirming evidence that, for radiation protection purposes, endosteal cells may be considered the only group of cells at risk of sarcoma induction by low doses of bone-seeking alpha emitters, whereas the role of marrow stromal (osteogenic) cells as target cells is much more significant with increasing intakes, and can become dominating if intake is high enough.

INTRODUCTION

Currently, the main source of data for assessing the risk of bone sarcoma due to internal α-emitters in humans is the results of epidemiological observation of humans with long-lived radionuclide burdens Ra-226 + Ra-228 [2]. Proceeding from the linear non-threshold conception, the International Commission on Radiation Protection (ICRP) [10] recommends to assumption of the risk coefficient for bone sarcoma in humans as equal to $10^{-2} \cdot Gy^{-1}$, if

alpha-particle dose is calculated for endosteal cells, which are located within 0-10 μm from bone surface. At the same time, ICRP has repeatedly emphasized that this model is intended to represent only the upper limit of risk, not the risk itself, and that the correct value probably lies somewhere between the linear extrapolation and zero [2]. In particular, the ICRP model would predict about 15 radiogenic bone sarcomas in a group of men with skeletal average doses not exceeding 10 Gy, where, in fact, no tumors, or other radiogenic effects, are observed.

Clearly, we need a theory of the long-term effects of radiation as a function of dose and dose rate in order to reduce the uncertainties involved in the assessment of sarcomogenic risk to man from deposited radioactivity.

The well-known theory of bone sarcoma induction by alpha emitters was developed by Marshall and Groer [13] as early as 1977. The important advantage of this theory is an attempt to link the process of osteosarcoma induction with the processes of bone remodeling. However, certain assumptions used in this theory should be revised in respect to current knowledge about the mechanism of cancer induction by radiation. In particular, one of the central postulates of the theory, "there are two initiation events produced by alpha radiation in a cell at risk which are necessary for osteosarcoma induction" [13], leads to a serious underestimation of the risk values predicted by the model.

We have recently constructed [17,18] a mathematical model for sarcomogenic action of alpha emitters similar to the model of Marshall and Groer. The main directions of theoretical development are: a more complete involvement of current knowledge on the mechanism of radiation cancer induction; and evaluation of the role of bone renewal in the process of sarcomogenesis. The model agrees with the data on bone sarcoma incidence in human-carriers of long-lived isotopes Ra-226 + Ra-228. Extrapolation of these data to low-intake region, using a theoretical approach developed, suggests that the linear ICRP-UNSCEAR model overestimates risk for bone sarcoma at low doses, possibly by a factor of 2-4. The model suggests the linear response of target cells to initiation effects of alpha irradiation. The nonlinear (linear-quadratic) initial part of the dose-response curve for osteosarcoma induction is explained quantitatively by model with the promotion role of regenerative hyperplasia resulting from inactivation effects of alpha radiation.

More recently, we introduced several additional assumptions into the model and derived improved descriptions of radiation-induced disturbances of osteogenic cell kinetics. In general, this description is consistent with the most advanced theories of tissue response to radiation developed in recent years [24,21]. However, this correction does not change significantly the main conclusions made on the basis of the developed theoretical approach.

We hope that our model will help describe many findings in sarcomogenesis induced by alpha and beta emitters in humans and animals and explain them quantitatively.

This presentation includes the general description of the theory developed and discussion of possible applications of the mathematical model of dose-response relationship based on the theory to the risk assessment.

ASSUMPTIONS OF THE MODEL

The model involves 10 main assumptions relating to:
1) mechanisms of (radiation) carcinogenesis;
2) target cells for sarcoma genesis and its location in bone;
3) cell and tissue kinetics in bone with or without irradiation.

Mechanism of (radiation) carcinogenesis

It is known [20] that carcinogenesis is a multistage process, which can be subdivided into three stages: initiation, promotion, and progression. Initiation is the event(s) induced by the carcinogen (radiation) which causes irreversible alterations in a normal cell and transforms it into a premalignant cell (initiated cell). At that moment, an initiated cell does not differ phenotypically from normal cells and retains all their properties. An initiated cell is converted into a malignant cell at the second, or promotion, stage under the influence of tumor promoters, which stimulate cell division. Malignant cells initiate the irreversible growth of tumors and their progression. The nature of initiation and promotion events is not yet known. However, for the construction of a dose-response relationship for cancer we can select, based on theoretical grounds, several principal assumptions consistent with current knowledge of the mechanism of radiation carcinogenesis and applicable to the induction of many types of tumors, including bone sarcomas.

Assumption 1: Premalignant genetic cell effects induced by radiation belong to a group of completed cellular end points [3, 22]

Assumption 2: Initiated cells do not differ phenotypically from normal cells and retain all their properties [20].

Assumption 3: An initiated cell is converted into a malignant cell through proliferation process [20].

(Assumption 1 (hypothesis) relating to the nature of initiation event in radiation carcinogenesis, which we and Sandberg [22] proposed earlier, is gaining more confirmation from recent data in the field of cancer cytogenesis and experimental findings concerning neoplastic cell transformation in vitro and also from the oncogene theory, as described in detail elsewhere [3].)

From assumptions 1-3, some general conclusions on the shape of dose-response relationship can be drawn:

1. Dose-response relationship for an initiated event in a cell must be a linear function of alpha-particle dose, i.e. that function which is characteristic of all types of cellular end points, induced by alpha radiation at least in a dose rate region (< 0.1 Gy/day) where individual alpha particles act independently (see assumption 1).

2: According to assumption 1, the initiation phase involves only one radiation-induced stage but not two equally important initiation events well separated in time which may be attributed to radiation.

3: According to assumption 3, the probability of conversion of an initiated cell into a malignant cell in vivo depends on the tissue turnover, which is considered in the model as a natural (radiation independent) tumor promoter.

4. Effects of radiation during the promotion stage can be developed via postirradiation repopulation, which accelerates normal cell division, including the rate of multiplication of the progeny of the initiated cell (see assumption 2).

For quantitative descriptions of the probability of conversion of an initiated cell into a malignant cell as one of the major parameters of our model, we have introduced a number of divisions among the progeny of the initiated cell. Therefore, the developed model

includes a description of tissue turnover, with and without irradiation, in which the rate of osteogenic target cell proliferation became the main parameter.

Target cells and their location in bone

Usually, osteogenic cells are considered as cells at risk for osteosarcoma induction, particularly those located on or near the endosteal surface of bone [9,11]. It is also known that, under abnormal conditions, some stromal cells of the bone marrow can be induced to produce bone forming cells [5,6]. These cells are frequently found within the range of alpha-particles. In cortical bone, such cells are lining the walls of the blood vessels of the Haversian canal [5]. In the description of our model, we will refer to these cells as (osteogenic) cells of the bone marrow. Moreover, the stromal cells of the bone marrow are likely to be the cells which are responsible for bone formation under conditions of intensive alpha irradiation resulting in a considerable or complete inactivation of endosteal cells.

For these reasons we assume that:

Assumption 4 - Cells at risk for induction of osteosarcomas are endosteal cells and osteogenic marrow cells. The latter are uniformly distributed within the marrow cavity and their concentration is substantially lower than that of endosteal cells.

Cell and tissue kinetics

In adult humans, the kinetics of osteogenic cells is associated with processes of bone remodeling: bone formation and resorption. The majority of the endosteal surface is always covered by a single layer of nondividing bone cells (lining cells). When a section of bone surface becomes the site of remodeling, endosteal cells are replaced by proliferating cells (preosteoblasts), which mature into the osteocytes of a new bone [6]. When the remodeling is complete, the new bone surface is covered by osteogenic cells again [6]: i.e., in terms of bone formation it becomes quiescent. Processes of resorption destroy bone tissue, removing endosteal cells from bone surface. Later, a new bone formation or apposition is started on the destroyed portions of the bone.
In the model for description of cell kinetics, we introduced the following main assumptions:

Assumption 5: Endosteal cells and marrow osteogenic cells are stem cells, which are capable of self-renewal and differentiation.

Assumption 6: The proliferative cells committed to differentiation are produced by stem cells. After several divisions, cells mature into the bone forming cells (osteocyte).

Irradiation effects on cell kinetics are introduced on the basis of the following additional assumptions:

Assumption 7: Radiation-inactivated (killed) stem cells remain in the stem cells compartment until they receive a signal to divide.

Assumption 8: Killed cells (with probability $p = 1$) die at the first attempted mitosis.

Certainly, radiation-inactivated cells do not necessarily die at first-attempted mitosis but may proceed successfully through several divisions before a lethal mitotic failure occurs. The probability of a successful mitosis of a cell which has lost its clonogenic potential is the smaller; the larger probability is the dose [24]. Therefore, Assumption 8, concerning the kinetics of killed cells in vivo should be regarded as oversimplification.

For estimation to what extent and through which mechanism marrow osteogenic cells may participate in the processes of bone formation, we introduced the following assumption:

Assumption 9: Marrow osteogenic cells are the reserve cells which are recruited to bone formation only after complete inactivation of endosteal cells takes place.

Finally, we introduced an assumption that osteogenic cells are mixed in bones due to their remodeling.

Assumption 10: Processes of skeletal remodeling (bone formation and resorption) lead to gradual intermixing of endosteal cells with marrow osteogenic cells.

FUNCTIONAL SCHEME

The functional scheme of the model formalizing the above discussed assumption, is presented in Fig. 1.* It reflects, with some degree of simplification, the processes in a bone structural unit (BSU) [19]).

BSU and its surfaces may exist in two states; quiescent (Q-state), and active (A-state), which consecutively and successively change each other. Q-state is characterized by two groups of non-proliferating cells (endosteal (M) and marrow osteogenic (N) cells). A-state is characterized by a self renewing pool (W) of osteogenic cells which is formed by endosteal cells and, in case of their considerable inactivation, by two other groups of cells; namely by a fraction (μ) of marrow osteogenic cells, and non-division population (V) of osteogenic cells, which is equal to (1 - μ) of the number of marrow osteogenic cells. When the remodeling is complete, osteogenic cells of W pool appear to be regularly distributed in the depth of endosteal surface.

In those areas of bones where alpha-emitters are located, irradiation of tissue leads to the appearance of a number of cells with premalignant damage (M*, N*). Irradiation also results in a reproductive death of some osteogenic cells (M1, N1). During transition of BSU from Q-state to A-state, the self-renewing population is formed near the bone surface in which the rate of cell division is determined by the rate of cell differentiation. In addition, cell-division is accelerated due to the death and subsequent loss of reproductively inactivated cells prompted to division.

Initiated cells and intact cells are equally involved in proliferation, and undergo the malignant transformation with the probability (α_0+dα), which is proportional to the mean number of division of osteogenic cells in A-state ($æ_0$+æ). This starts the irreversible process of tumor development.

MATHEMATICAL FORMULATION OF THE MODEL

For mathematical formulation of the model, we have introduced the following notations. Let {Sj} denote the natural distribution of endosteal cells (Mo = S1) and marrow osteogenic cells (No = S2 + S3 + ...) in BSU as a function of distance from bone surface, where Xoj is

the number of normal osteogenic stem cells in j-layer at distance hj from bone surface.

Let also {Xoj}, {Xo1} and {X*j} denote the same distribution for normal (intact), inactivated (killed) and initiated osteogenic stem cells, respectively. Let Fj denote dose rate of irradiation of osteogenic cells located within a thin layer at distance hj from bone surface.

Let Wo, W1 and W*, respectively, denote the number of normal, inactivated and initiated cells in self-renewing pool of the osteogenic cells. Let hw denote effective distance from bone surface where these cells lie. Let Fw denote exposure rate of these cells.

Let To denote the average time during which Q-state is maintained on and near bone surface of BSU while Ta is the same for A-state. Then Tc = To + Ta is the mean interval between periods of remodeling on BSU in question. Let tn denote the time between the beginning of alpha emitter intake and establishment of Qn-state in BSU, i.e., tn = n (To + Ta) or it equals n To.

Equations for description of cell kinetic

The kinetics of osteogenic cell population at Q- and A-state is described by the following system equations, respectively:

$$dXoj/dt = - k\,Fj\,Xoj \quad ; \qquad (j = 1,N) \qquad (1)$$
$$dX^*j/dt = (\sigma/k)\,k\,Fj\,Xoj - k\,Fj\,X^*j \quad ,$$

$$dWo/dt = \rho\,Wo\,(S - Wo - W1) - \lambda\,Wo\,(Bo - Wdif) - k\,Fw\,Wo;$$
$$dW1/dt = - \rho\,W1\,(S - Wo - W1) - \lambda\,W1\,Bo - Wdif) + k\,Fw\,Wo;$$
$$dWdif/dt = \rho\,Wo\,(Bo - Wdif); \qquad (2)$$
$$dW^*/dt = (\sigma/k)\,k\,Fw\,Wo + W^*\,[(1/Wo)\,dWo/dt\,] - a\,W^*,$$

where σ is the probability of an initiation event per cell per unit of alpha-radiation dose; k is the probability of killing (reproductive death) osteogenic cells per unit alpha-radiation dose; ρ is maximum division rate of osteogenic cells; λ is differentiation rate of osteogenic cells; S is the number of osteogenic cells involved in self-renewing population cells (S = Wo + W1); Bo is the total number of stem cells which differentiate during A-state and which are necessary for completing processes of bone formation; Wdif is current number of committed osteogenic cells;

Let Xoj(tn) and X*j(tn) denote the distribution of intact cells to moment tn. Then, solving the system (1), we get easily that to time (tn + To):

$$Xoj(tn+To) = Xoj(tn) \exp(- k\ Fj\ To), \qquad (j = 1,N) \qquad (3)$$

$$X^*j(tn+To) = [\sigma\ Fj\ Xoj(tn) + X^*j(tn)] \exp(-k\ Fj\ To) \qquad (4)$$

The number of osteogenic cells involved in self-renewing pool W is defined by the following condition:

$$Wo(tn+To) = \sum_{j=1}^{L} Xoj(tn+To) > Wmin \qquad (5)$$

where Wmin is a critical number of surviving cells, e.g., the number of cells necessary for prevention of focal destruction of stem cell compartment. According to assumption 9, L is a minimum number for which condition (5) is fulfilled. Solving numerically the system (2) with the initial conditions

$$Wo(tn+To) = \sum_{j=1}^{L} Xoj(tn+To), \quad W^*(tn+To) = \sum_{j=1}^{L} X^*j(tn+To), \quad S = \sum_{j=1}^{L} Sj,$$

we determine the number Wo and W* of cells at the moment tn+To+ta=tn+1. We could note that at the value of Bo parameter lower than unity the number of cells Wo does not reach the normal level So*) at any time.

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*) It can be shown that system (2) has a simple solution if Bo>>1: $Wo(tn+1)=So$ and $W^*(tn+1)=W^*(tn+To)\ So/Wo(tn+1) + \sigma\ Fw\ So\ Ta$

During the transition to a Q-state, osteogenic cells of W pool are regularly redistributed in a natural way in the depths from the endosteal surface. Processes of resorption and apposition lead to a partial intermixture which may be accounted for by the following equations:

$$Xoj(tn+1) = Sj * q, \qquad (7)$$

$$X^*j(tn+1) = Sj * q^*, \qquad (8)$$

where

$$q = Wo(tn+To)/So\ (1 - n\ (1 - So\ )) + Vo(tn+To)\ n\ , \quad (9)$$

$$q^* = W^*(tn+To)/So\ (1 - n\ (1 - So\ )) + V^*(tn+To)\ n\ , \quad (10)$$

$$Vo(tn+To) = \sum_{j=l+1}^{N} Xoj(tn+To), \quad V^*(tn+To) = \sum_{j=l+1}^{N} X^*j(tn+To)$$

Here, q is the total number of inactive osteogenic cells at time moment tn+1, and q* is the number of initiated cells. At a complete cell intermixture ($\upsilon = 1$) $q = Wo(tn+1) + Vo(tn+To)$ and $q^* = W^*(tn+1) + V^*(tn+To)$. The obtained distributions Xoj(tn+1) and X*j(tn+1) determine the initial conditions for Q(n+1)-state.

Incidence of bone sarcoma

According to assumption 3, the probability of tumor development from an initiated cell is proportional to the rate of osteogenic cell division which here is equal to the number of cell divisions in a certain time. During the A(n) state of BSU, the mean number of osteogenic cells division is equal to

$$æ_n = æ_o + [Wo(tn+To+Ta) - Wo(tn+To)] * \exp(- \lambda v\ tn\ ), \quad (11)$$

where $æ_o$ is the mean number of osteogenic cell divisions during A-state in intact bone, aimed at compensation of cells bounded to is differentiation, $æ_o = Bo$;

[Wo(tn+1)- Wo(tn+To)] is the number of divisions induced by the death of cells which have lost the property of unlimited proliferation but underwent mitosis; numerically, it is equal to the increase in the cell number Wo during A-state;

$\exp(-\lambda vtn)$ is the fraction of bone tissue incorporating alpha emitters; parameter λv is equal to the bone resorption rate if we deal with a single intake and equal to O (and therefore $\exp(-\lambda vtn) = 1$) for prolonged intake.

Taking into consideration equations (1-11), the cumulative incidence of osteosarcomas between the start of alpha-emitters accumulation and time (t+g) is defined as follows:

$$I(t+g) = C \left[\sum_{n=1}^{m} W^*(tn+1)\ æ_n + W^*(tn+2)\ æ_{n+1}\ (t-m) \right], \quad (12)$$

where g is the time of tumor growth, i.e., the time since malignant transformation of the initiated cell to the appearance of the detectable tumor; m is the whole part of t/(To+Ta) value; C is the product of multiplication of (r/k)•Sabs•ao, where Sabs is the total number of endosteal cells in intact bone; ao is the probability of conversion of an initiated cell into a malignant one per cell division; (r/k) is the ratio of probabilities of initiation and inactivation by alpha irradiation.

Note that the second term in Eq. 12 represents the contribution to the total frequency of tumor induction in those parts of bone surface which have been involved in A(n+1)-state at time t. We should also note that, for voluntarily chosen BSU, the mean interval for the Q(1)-state is equal to To/2.).

PARAMETERS OF MODEL

The model incorporates two group parameters: "theoretical" and "free" ones. The first group parameters may be estimated on the basis of the available biological data. The qualitative properties of interest here are not critically dependent on the numerical values assigned to these parameters. The second group parameters would be adjusted by statistical treatment of observed dose-response relation in order to obtain its "best" fit.

Theoretical parameters

1. Ta is the average time during which on and near bone surface of BSU A-state is maintained (Ta = 60 days).

It appears that value Ta can be evaluated on the basis of osteon development time in human cortical bone, which is equal to 6-8 weeks [6].

2. To is the mean time during which BSU is maintained in Q-state (To = 2 years).

The time To can be roughly equal to the mean interval between periods of remodeling at the average bone surface, which in its turn

is determined by the rate of surface turnover (λs), and not by the rate of bone turnover (λv) (for adult man $\lambda v = 0.1$ year^{-1}). The difference is determined by the depth effect, i.e., a typical depth of resorption or width apposition (d) considerably smaller compared to the width of the trabeculae, because the trabeculae usually consists of several layers of bone tissue, pertaining to different bone generations. Therefore, we have assumed that To = 2 years.

3. q is the ratio of concentrations of osteogenic cells in bone marrow and endosteal layer (q = 0.1).

The osteogenic cell concentration in bone marrow appears to be substantially lower than that on and near the endosteal surface. For this calculation, we assume that q = 0.1. Then the ratio of a total number of cells in bone marrow (N) to that in endosteal layer (M) would be equal to 2.5 if we assume that the weight of the endosteal layer (10μm) and bone marrow are equal, respectively, to 60 g and 1500 g [11]. Then the total number of osteogenic cells would be equal 3.5 M.

4. Wmin is a critical number of surviving cells, e.g., the number of cells necessary for prevention of focal destruction of stem cell compartment (Wmin = 0.05 So).

5. λ is the rate at which stem cells of self-renewing pool differentiate during A-state (λ = 0.1 1/day).

Value for λ appears to be within interval $bo/Ta < \lambda < \rho$.

6. ρ is a maximum division rate of osteogenic cells in vivo (ρ = 1 1/day [5]).

7. hw is the average distance from bone surface, where the self-renewing pool is located (hw = 30-40 μm [9]).

8. α is the rate of normal cell loss from self renewing pool. (α = 0.05 1/year).

Based on Ra-224 data [14] related to the dynamic of tumor development, we assume that α = 0. 05 1/year.

9. υ is the parameter which characterizes the degree of the intermixture of osteogenic cells in bone ($\upsilon = 0.5$).

10. g is the time for tumor growth in human (q = 5 years [13]).

11. k is the probability of an inactivation (reproductive death) of cell per unit of alpha radiation dose (k = 1.7 1/Gy [12]).

12. F is the dose rate of alpha irradiation of osteogenic cells. The dose rate (Gy/year) to osteogenic cells from a uniform volume deposit of Ra in bone is:

$$F(t,h) = r\ kv\ \eta v(h)\ A\ f1\ Rv(t)\ M_{body}/M_{bone}$$

where $\eta v(h)$ is the ratio of the dose rate at distance h from endosteal surface to that within bone. A is a single intake of radionuclides by ingestion, Bq/kg body weight; f1 is the fraction of ingested intake absorbed into the blood (f1= 0.2 [11]); Rv(t) is the retention function for radium in trabecular (cortical) bone as function of the time t after the start of a single intake [9]; M_{body} is human body weight (M_{body} = 70 kg [11]); M_{bone} is trabecular bone weight (M_{bone} = 1 kg [9]) or cortical bone weight (M_{bone} = 4 kg [9]); Kv = $6.2 \cdot 10^{-5}$ Gy/year Bq/kg for α-emitters Ra-226 and$14.4 \cdot 10^{-5}$ (for Ra-228); r is the dose correction factor (r = 0.5).

"Free" parameters

1. C = (σ/k) Sabs αo i.e., parameter C is the product of multiplication of $(r/k) \cdot$ Sabs$\cdot$ao, where Sabs is the total number of endosteal cells in intact bone; ao is the probability of conversion of an initiated cell to a malignant one per cell division; (r/k) is the ratio of probabilities of initiation and inactivation by alpha irradiation.

2. Bo = æo is the physiologically normal number of osteogenic cell division during one cycle of remodeling bone surface (or in terms of the model, during A-state), aimed at compensation of cells destined for differentiation.

Note that within the framework of the model, parameter C plays the role of an arbitrary scaling constant that determines the absolute

incidence of osteosarcomas, while parameter Co is influencing the value of initial slope of the dose-response curve for bone sarcomas.

FITTING THE MODEL TO DATA FOR RA-226 + RA-228 IN MAN

Data Sets Used

Epidemiological data [1] concerning induction of bone sarcomas in humans with incorporated long-lived isotopes Ra-226 and Ra-228 cover a considerable number of individuals (over 2000), who have now been followed for more than five decades. In particular, this cohort includes a large group of dial painters. The Ra-226 and Ra-228 body burdens were measured in most of the individuals and the initial skeletal uptake was estimated using Norris' empirical retention function for radium in man [1]. Among individuals with measured body contents of radium, 60 bone sarcomas occurred by 1978 [1]. One more case of bone sarcoma was discovered by 1985 [15].

From the total number of cases, we selected 486 with intakes of Ra-226+Ra-228 higher than $3.7 \cdot 10^3$ Bq/kg (0.1 μCi/kg) body weight, which is taken as 50 kg for females and 70 kg for males. Table 1 presents the selected cases arranged into 10 groups with different total radium intakes. It is interesting to note that 565 such cases were selected by us (see table 2) for which we calculated the initial skeletal uptake using retention function for radium in man from ICRP Publication 20 .

The expected number of osteosarcomas Pk in each of the selected groups K was calculated as follows:

$$Pk = \sum_m pkm = \sum_m Ikm(A6,A8,tm,twwed), \qquad (14)$$

where Ikm is the expected probability of bone sarcoma induction for individual M of group K. According to equation (12), the probability Ikm was calculated separately for each individual, taking into account the estimated intake Ra-226 and Ra-228 (A6 and A8, respectively), rate of intake (td) and the duration of observation (tm).

Estimation of the free parameters

The model (Eq. 16) is fitted by maximum likelihood to data in the grouped format described above (table 1). The maximum likelihood estimates of parameters C and bo is bo = 0.3 and C = $9.3 \cdot 10^{-2}$. Fixing consecutively one of parameter bo or C, and varying another, we estimated 70% confidence area of parameters value, which is bo (0.1 - 0.7) and C ($1.31 \cdot 10^{-2}$-$6.3 \cdot 10^{-2}$) with F-criteria.

The expected number of bone sarcomas in each selected group K calculated by our model with parameter b = 0.3 and C = $9.3 \cdot 10^{-2}$ (P= 0.85), are given in tables 1 and 2. The resulting curve is presented on Fig. 1.

Analysis of parameters

Although all independent parameters are estimated on biological consideration they, excluding parameters To and Wmin, do not influence the estimation of "free" parameters Bo and C. However, a more correct estimation of some of them may be necessary for describing other data, for example, the well-known Ra-224 data.

APPLICATION TO RISK ASSESSMENT

Having estimated the free parameters, we can calculate the model dependence of bone sarcoma rate as a function of time-since-intake for various total intakes and intake-rate regimens.

For example, Fig. 2 shows the cumulative incidence during 30 years in humans with various single intakes of Ra-226 by ingestion, calculated using our model (curve 1) and also the Marshall and Groer model [13] (curve 2). The region where osteosarcomas are observed (the circles on Fig. 2) are identically described by both models. However, extrapolated model curves differ substantially: the first is linear-quadratic and the second is purely quadratic.

The non-linearity of the initial part of the dose-response curve for osteosarcoma induction is explained quantitatively by a model with the auto-promotion role of radiation expressed via cell death-induced compensatory hyperplasia. This excessive (versus the physiological baseline) proliferation of osteogenic cells, increasing the probability of initiated cell conversion into malignant cells, pre-determines the transformation of linear dose-response curves, due to single-stage

initiation, into linear-quadratic function. (Note. This explanation coincides completely with the initiation/promotion theory of induced carcinogenesis, radiation exerting influence on both the initiation and promotion stages. Recently, an analogous quantititative explanation of the non-linearity dose response relationship for induction of lung cancer has been suggested [7,23]). However, we succeeded also in a quantitative description of the curve of interest introducing in the model cell characteristics and tissue kinetics with and without irradiation].

Within the framework of the model, the degree of non-linearity of the initial range of dose-response relationships of interest is greatly influenced by the physiologically normal rate of osteogenic cell division in processes of bone remodeling. For very slow turnover tissue, this relationship becomes linear-quadratic, whereas for a larger one it would tend to become linear. It is known that stromal osteogenic cells are characterized by slow turnover of cell population. According to [4,6], these cells pass through only a few divisions during their lifetime. The rate of division of osteogenic cells appears to be the same. Let L be the number of osteogenic cell divisions in human life span (70 years). Then æo = [L*(M+N)/N]/ [70/(To+Ta)] and for L = 1 æo = 0.1. Thus, the lower estimation for parameter Bo, which was previously obtained empirically (Bo= 0.1-0.7), is in good accord with the estimation based on fundamental knowledge of tissue turnover in bone.

ESTIMATION OF MAXIMUM "LEOF" VALUE

Having received the estimation of the parameter Bo which, as shown above, is well based in the framework of the model, we can, on theoretical grounds, determine the limit of the ratio of bone sarcoma risks per unit dose at high and low level of radioactivity intake, which has also been called a linear extrapolation overestimation factor (LEOF).

According to our model (see Fig. 3), the most probable value of LEOF, estimated by maximum likelihood method is equal to 2.0 with 70% probability ranging from 1.6 to 4.3.

We also succeeded in evaluation of the upper theoretical estimate of this value. It may be calculated if we take into account only the promotion effect of alpha irradiation, without considering the role of initiated cell motivation. In this case, non-linearity of the curve of

interest results from auto-promotion only.

According to Eq.(11) "artificial" curves can be described as

$$I = A \sigma F \{Bo + [Wo - Wo * \exp(-kFTo)]/S\} \qquad (15)$$

where A is a constant; Wo is the number of intact osteogenic cells at the beginning of A-state; S is the total number of cells in self renewing pool of osteogenic cells; exp(-kFTo) is the fraction of cells which survive during Q-state.

For lowest intake $I = A \sigma F^* Bo$, while for relatively high intake (kFTo > 1-2) Wo = S, and then $I = A \sigma F * (Bo + 1)$. [Therefore, the LEOF value equals (Bo + 1)/Bo. For Bo = 0.3 (0.1 - 0.7) we find that LEOF = 4 (3-11). Uncertainty in estimation of LEOF value is associated with Bo evaluation on epidemiological data].

The resulting "artificial" curve is presented in Fig. 4. The upper theoretical limit of LEOF estimated from this plot is about $1.0 \cdot 10^{-2}$ Gy/11. This figure also determines the lower theoretical limit of the expected carcinogenic risk, which is equal to $1.0 \cdot 10^{-2}$ Gy/11.

Thus, as follows from our theoretical consideration, the possible range of risk diminution per unit of intake varies between 1.6 and 11. It should be noted that this range is the widest within the framework of our model.

The role of marrow osteogenic cells in sarcomogenesis

Curves "a" and "b" in Fig. 5 describe the contribution of endosteal and osteogenic marrow cells to total incidence of tumor. At low intake (kFoTo << 1), endosteal cells appear to be the main cells at risk because they accumulate the largest dose. At relatively high intakes (kFoTo >> 1), endosteal cells during Q-state are significantly inactivated by alpha emitters. Therefore, the role of marrow osteogenic cells as target cells is much larger at higher intakes, and it can become dominating if the level of intake is high enough. Hence, the model gives confirming evidence that, for radiation protection purposes, endosteal cells may be considered as the only group of cells at risk of sarcomagenesis induced by low doses of bone-seeking alpha emitters.

CONCLUSION

A theory of bone sarcoma induction by bone-seeking alpha emitters based strictly upon biological considerations is proposed.

The model suggests a linear response of target cells to initiation effects of alpha irradiation. The non-linear (linear-quadratic) initial part of the dose-response curve for osteosarcoma induction is explained qualitatively by the model with the promotion role of regenerative hyperplasia resulting from inactivation effects of alpha radiation.

According to the model, the most probable value of LEOF (linear extrapolation overestimation factor) is equal to 2.0, with 70% confidence interval, ranging from 1.6 to 4.3. The upper theoretical limit of LEOF is about 11. Thus, as follows from our theoretical consideration, the possible range of risk diminution per unit of intake varies between 1.6 and 11. It should be noted that this range is the widest within the framework of our model.

The model gives confirming evidence that, for radiation protection purposes, endosteal cells may be considered the only group of cells at risk of sarcomagenesis induced by low doses of bone seeking alpha emitters. However, the role of marrow stromal (osteogenic) cells as target cells, is increased by the higher intake and can become dominating if the intake is high enough.

We hope that our model is useful for describing many findings pertaining to sarcomogenesis induced by alpha and beta emitters in humans and animals and explaining these findings quantitatively.

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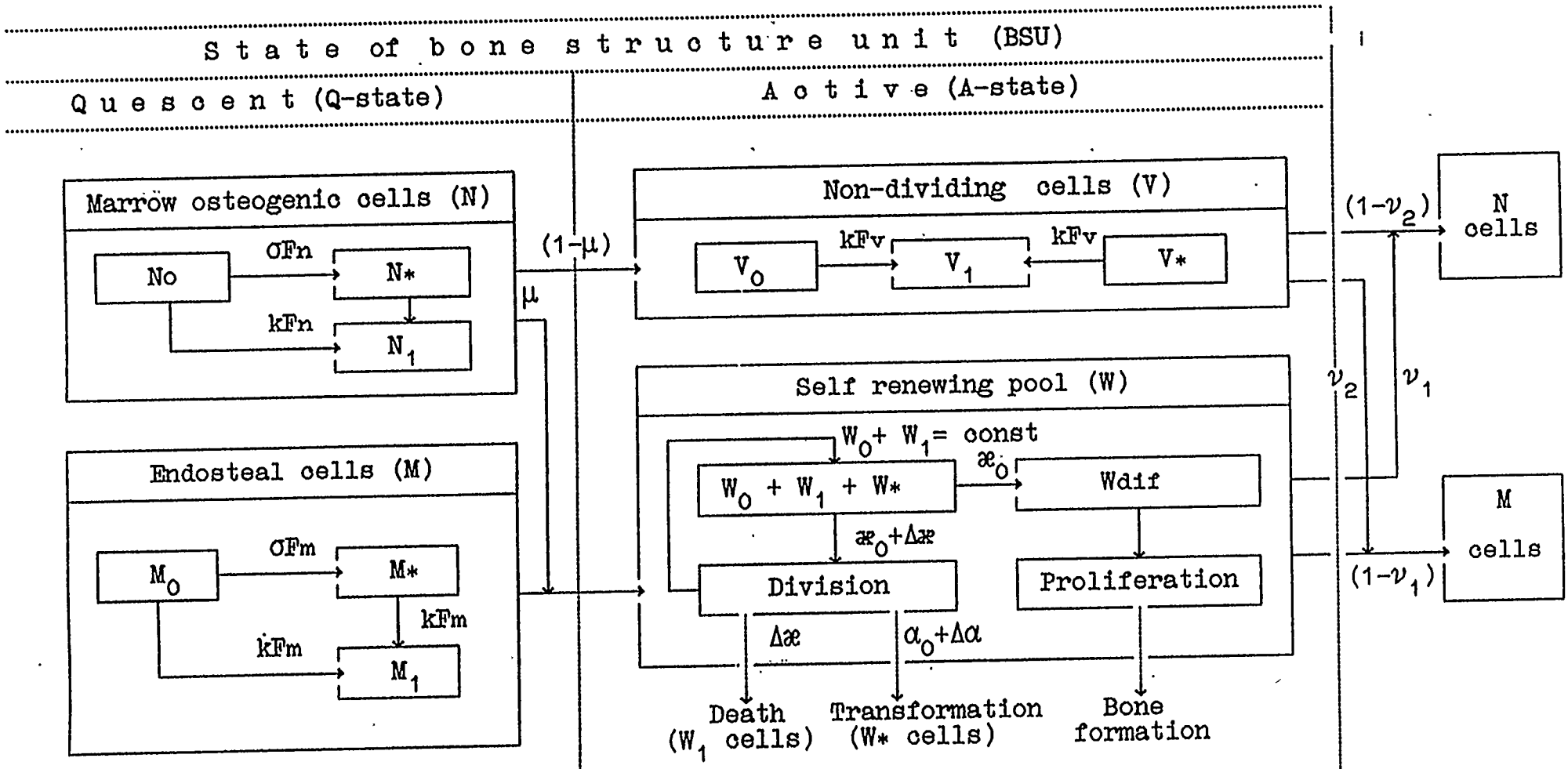


Fig.1*. Functional scheme of bone sarcoma induction by alpha emitters.

TABLE 1

OSTEOSARCOMA INCIDENCE IN RA-226 + RA-228 HUMAN-CARRIERS

GROUPS	ACTIVITY (*) μCi/kg	THE NUMBER OF PERSON	THE NUMBER OF OSTEOSARCOMAS	
			OBSERVED	EXPECTED (**)
1	100 - 71.8	1	1	0.12
2	71.8 - 27.0	34	10	11.8
3	27.0 - 13.8	33	11	11.5
4	13.8 - 7.18	40	13	13.8
5	7.18 - 3.37	66	19	15.3
6	3.37 - 2.70	20	3	2.30
7	2.70 - 1.38	41	3	2.64
8	1.38 - 0.52	70	1	1.81
9	0.52 - 0.27	66	0	0.76
10	0.27 - 0.10	127	0	0.53
	TOTAL	498	61	60.6

* RA-226 + RA-228 total activity uptake into the blood restored using Norris' retention function

** For bo = 0.3 and C = 9.3 10-2 (P > 0.85)

T A B L E 2

OSTEOSARCOMA INCIDENCE IN RA-226 + RA-228 HUMAN-CARRIERS

GROUPS	ACTIVITY (*) μCi/kg.	THE NUMBER OF PERSON	THE NUMBER OF OSTEOSARCOMAS	
			OBSERVED	EXPECTED (**)
1	100 - 71.8	3	1	1.28
2	71.8 - 27.0	40	12	11.7
3	27.0 - 13.8	43	15	13.7
4	13.8 - 7.18	58	16	16.9
5	7.18 - 3.37	56	12	9.58
6	3.37 - 2.70	18	2	1.68
7	2.70 - 1.38	47	2	2.70
8	1.38 - 0.52	86	1	1.87
9	0.52 - 0.27	70	0	0.64
10	0.27 - 0.10	122	0	0.43
	TOTAL	543	61	60.5

* RA-226 + RA-228 total activity uptake into the blood restored using ICRP retention function (ICRP Publication N 20)

** For bo = 0.3 and C = 7.4 10-2 (P > 0.9)

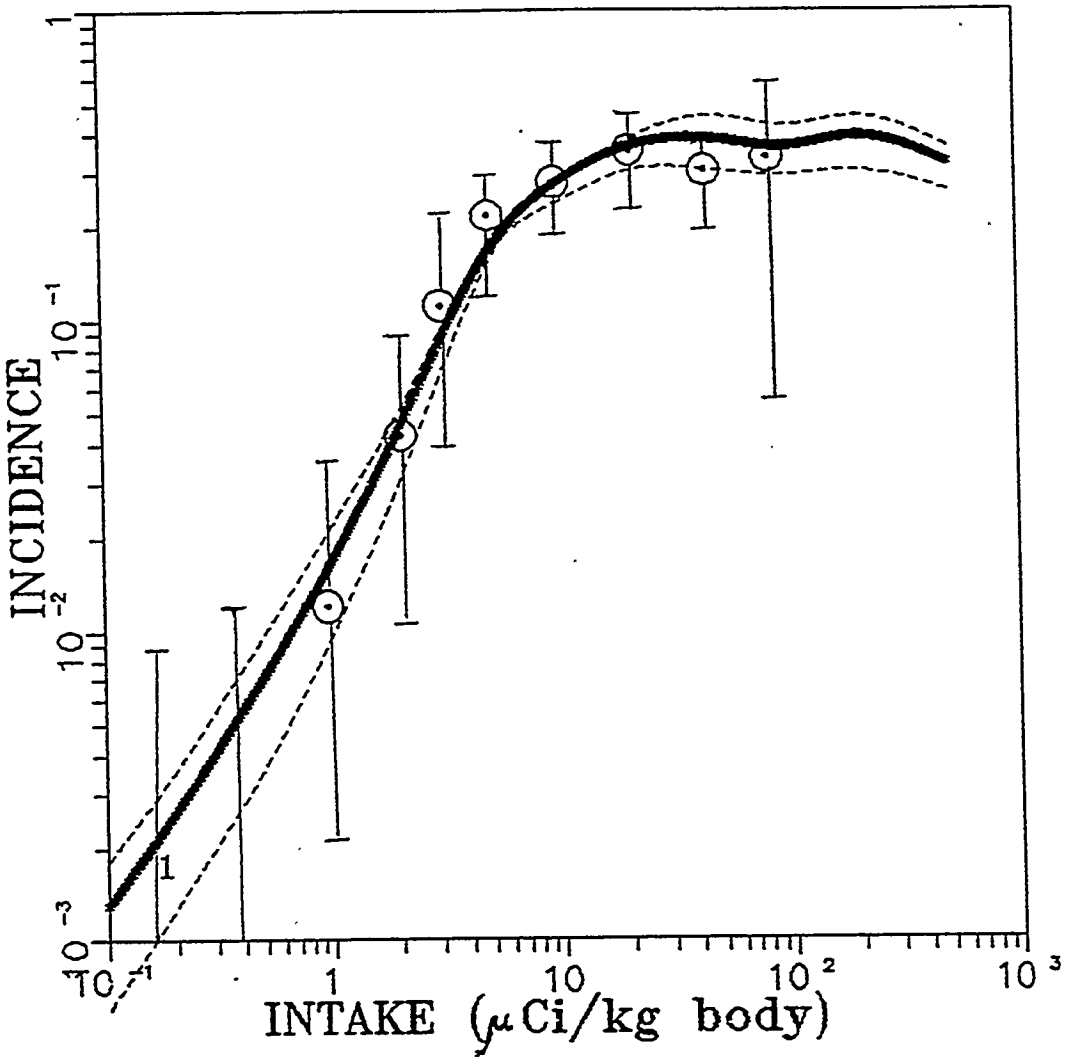


Fig.1 The cumulative incidence of of osteosarcomas in man vs the total intake (microcuries per kilogram body weight) of Ra-226 + Ra-228 as of December 31, 1978
1 - model curve with parameters Bo=0.3 and C=0.093 (maximum likelihood estimates). Dashed lines are model curves with upper and low bounds of parameter values Bo and C corresponding to 70% confidence area.

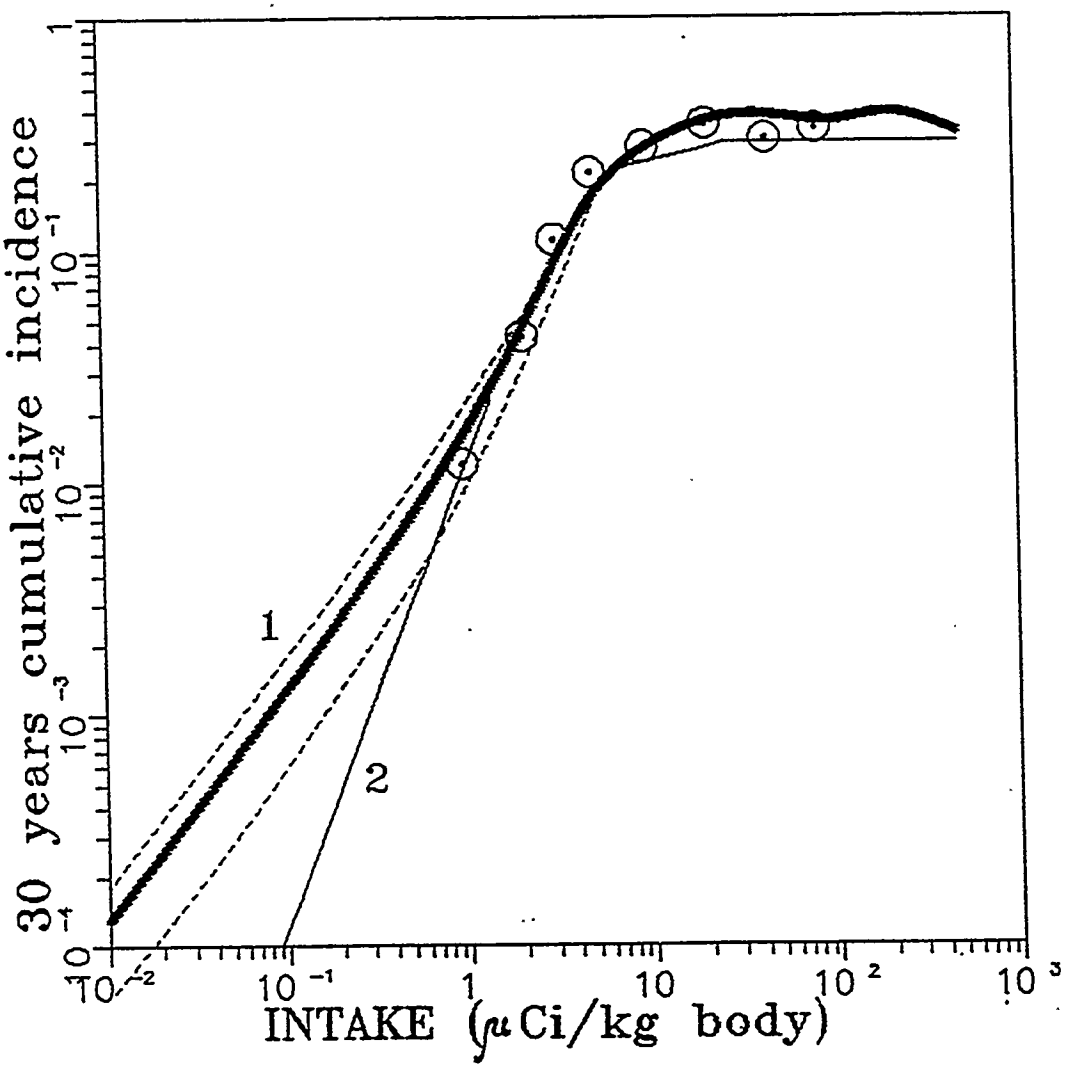


Fig.2 Bone sarcoma incidence versus Ra–226 single intake.

1 – model curve with parameters Bo=0.3 and C=0.093 (maximum likelihood estimates). Dashed lines are model curves with upper and low bounds of parameter values Bo and C corresponding to 70% confidence area.
2 – evaluation by Marshall and Groer model.
The circles present Ra–226 + Ra–228 data.

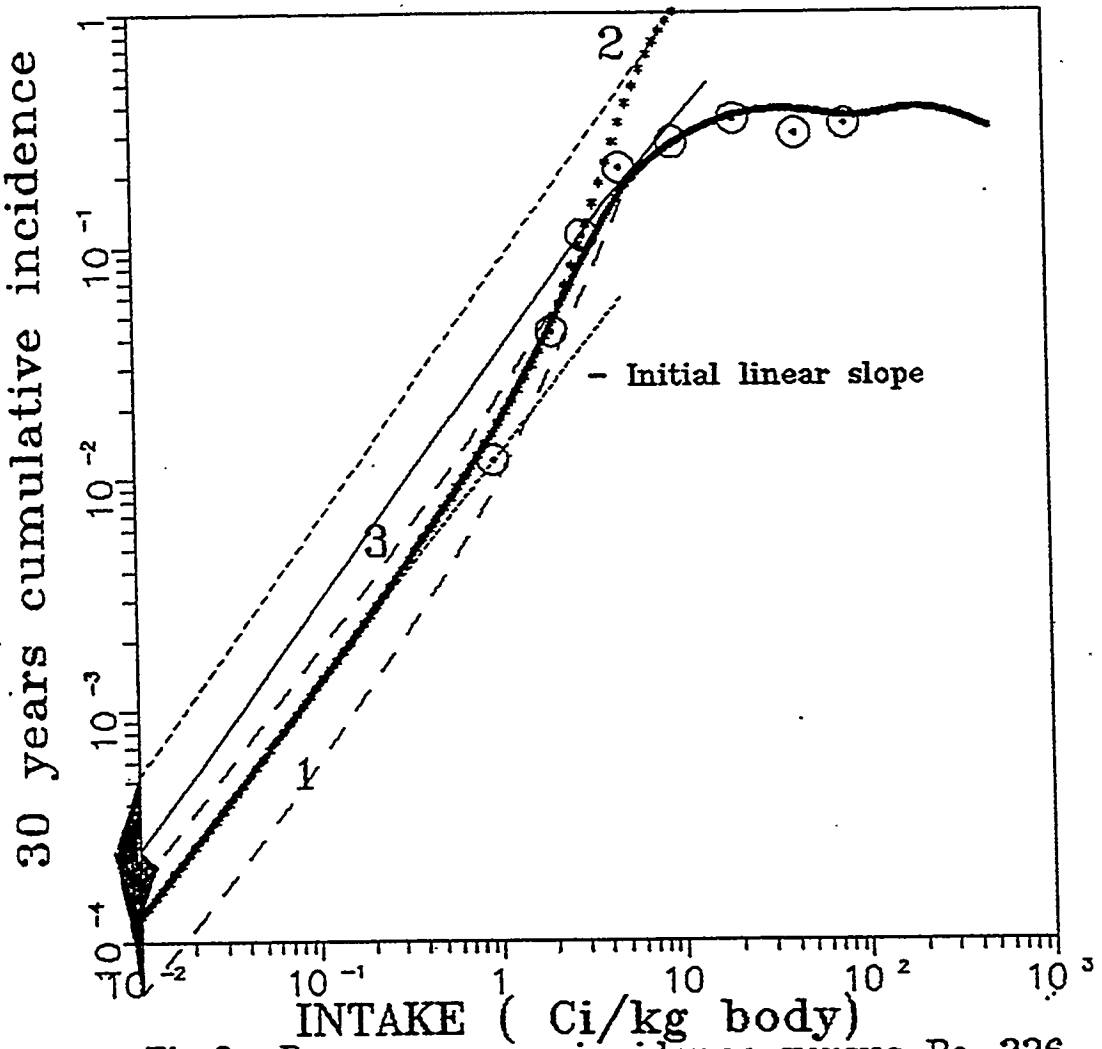


Fig.3 Bone sarcoma incidence versus Ra–226 single injection.

1 – model curve with parameters Bo=0.3 and C= 0.093 (maximum likelihood estimates).

2 – model curve not considering the role of initiated cells inactivation.

3 – Linear model.

▶ – The length at this section is the most probable LEOF value (Linear Extrapolation Overestimation Factor.

◀ – theoretically predicted maximum possible LEOF value.

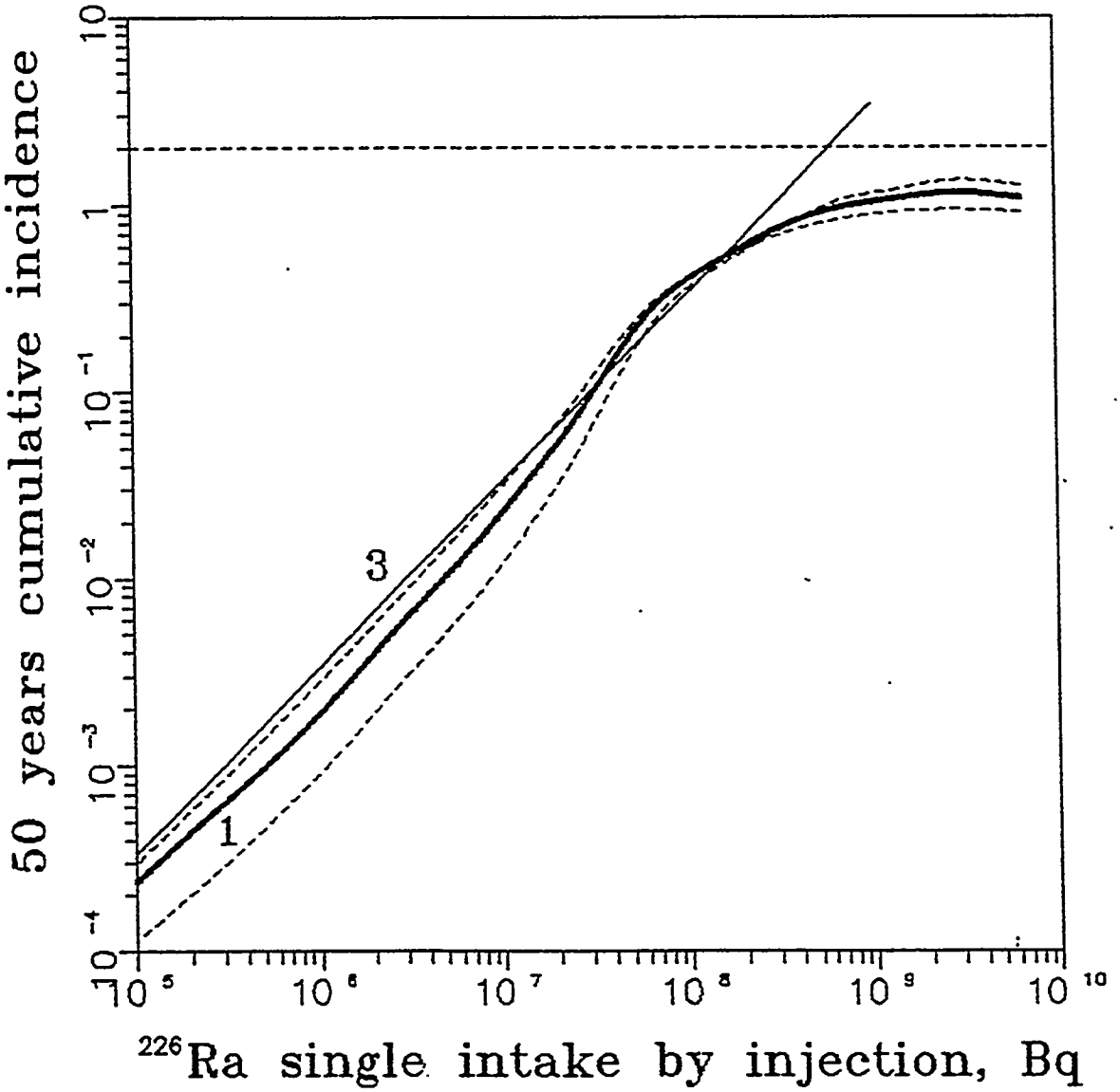


Fig. 4 Bone sarcoma incidence versus Ra-226 single injection.
1 - model curve with parameters Bo=0.3 and C= 0.093 (maximum likelihood estimates).
Dashed lines are model curves with upper and low bounds of parameter values Bo and C corresponding to 70% confidence area.
3 - Linear model (the line slope 3.4e-09 Bq^{-1}).

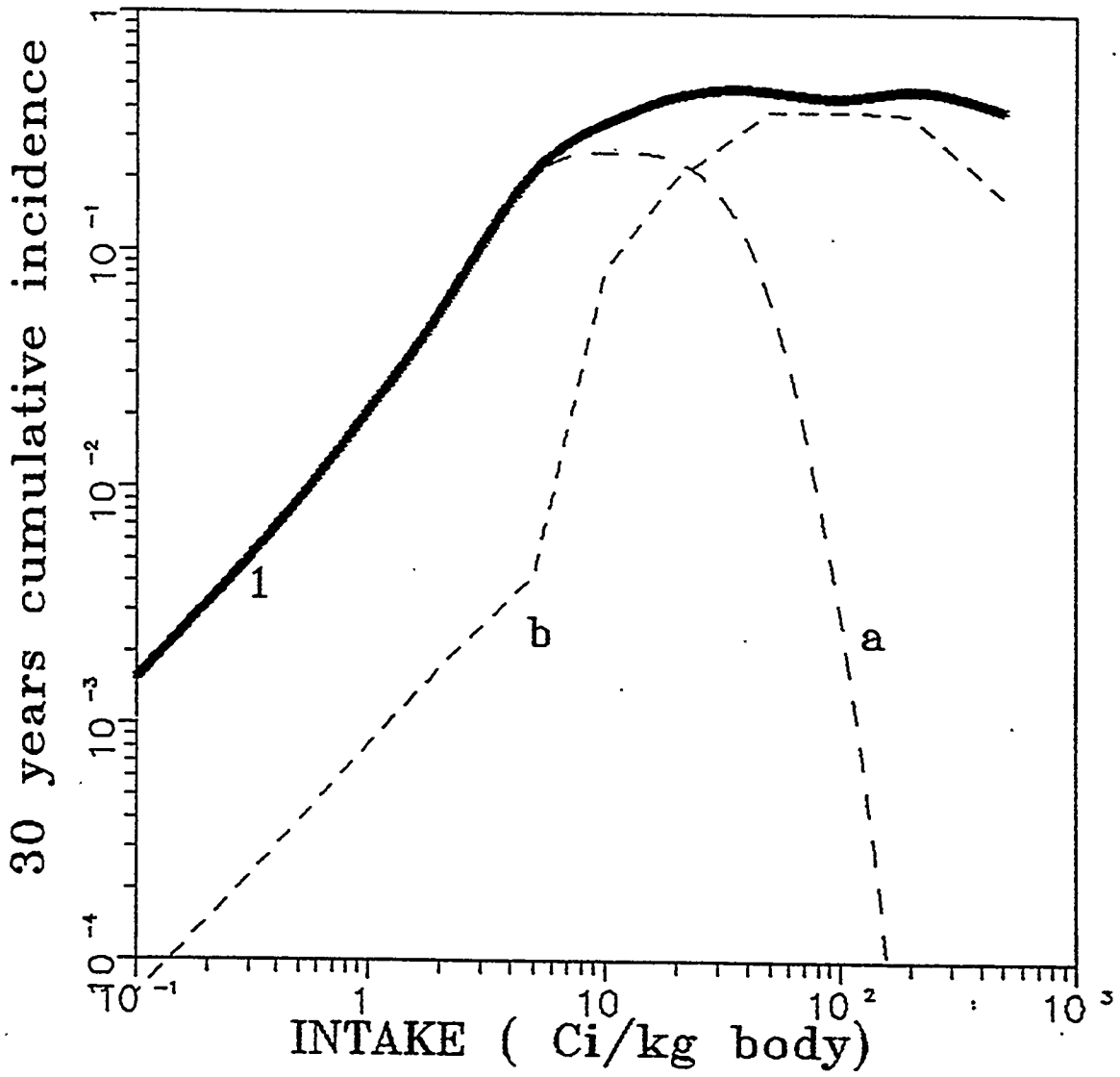
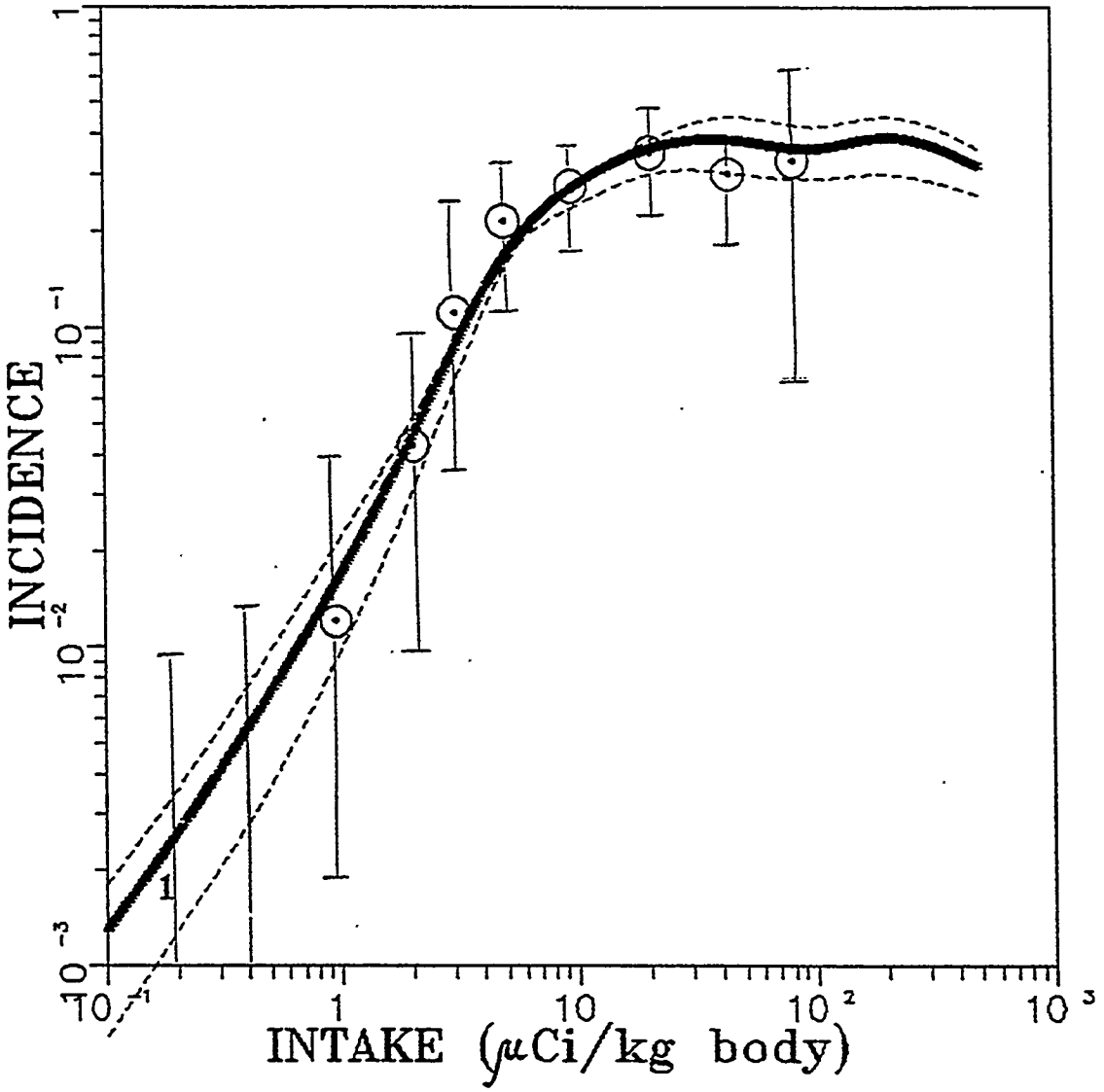


Fig.5 Bone sarcoma incidence versus Ra-226 single intake.
1 - model curve with parameters Bo=0.3 and C= 0.093 (maximum likelihood estimates).
a and b is a contribution to the total yield (curve 1) due to endosteal cells and marrow osteogenic cells exposure to alpha particles, respectively.



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1 - model curve with parameters Bo=0.3 and C=0.093 (maximum likelihood estimates). Dashed lines are model curves with upper and low bounds of parameter values Bo and C corresponding to 70% confidence area.

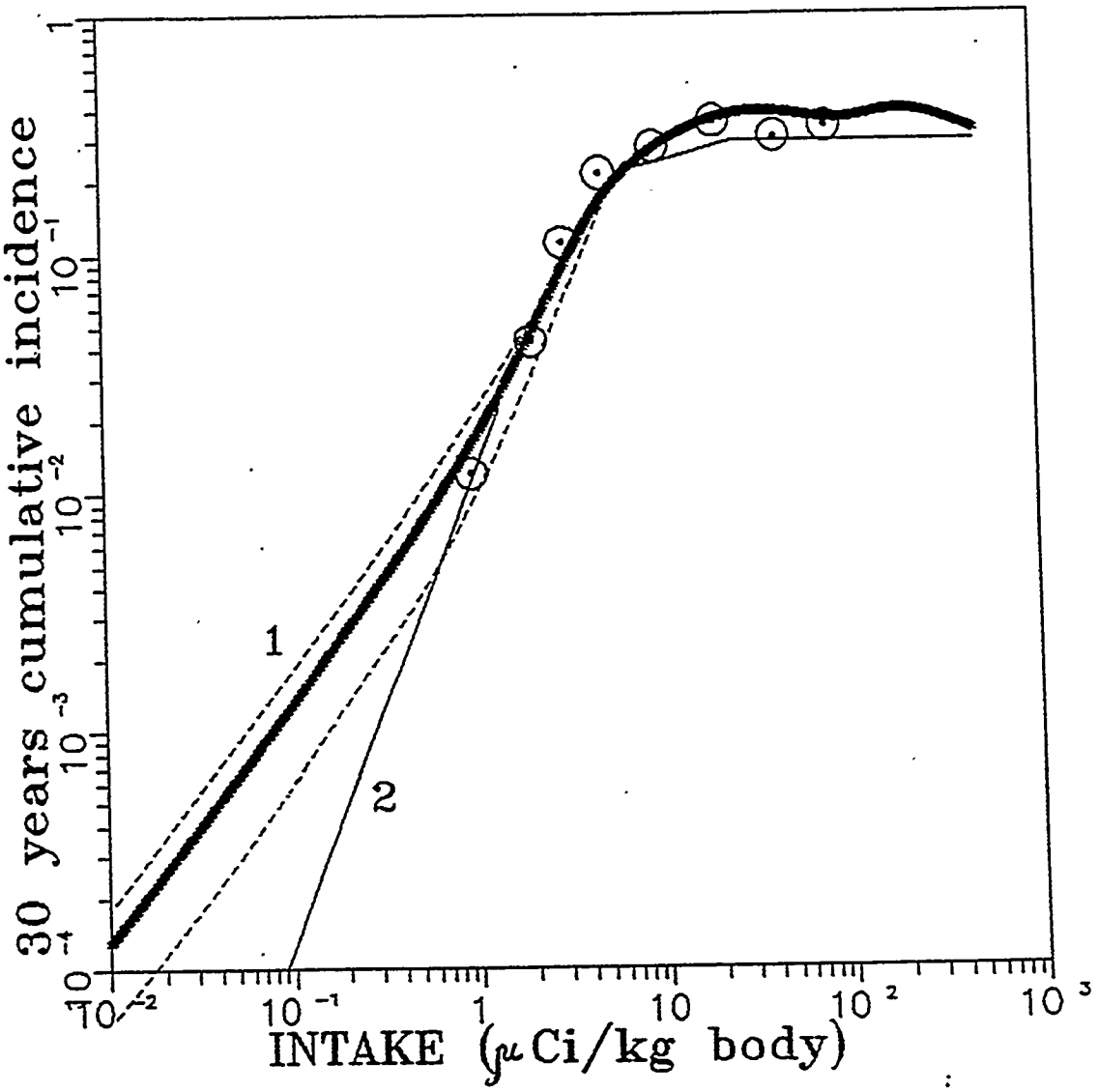


Fig.2 Bone sarcoma incidence versus Ra–226 single intake.

1 – model curve with parameters Bo=0.3 and C=0.093 (maximum likelihood estimates). Dashed lines are model curves with upper and low bounds of parameter values Bo and C corresponding to 70% confidence area.
2 – evaluation by Marshall and Groer model.
The circles present Ra–226 + Ra–228 data.

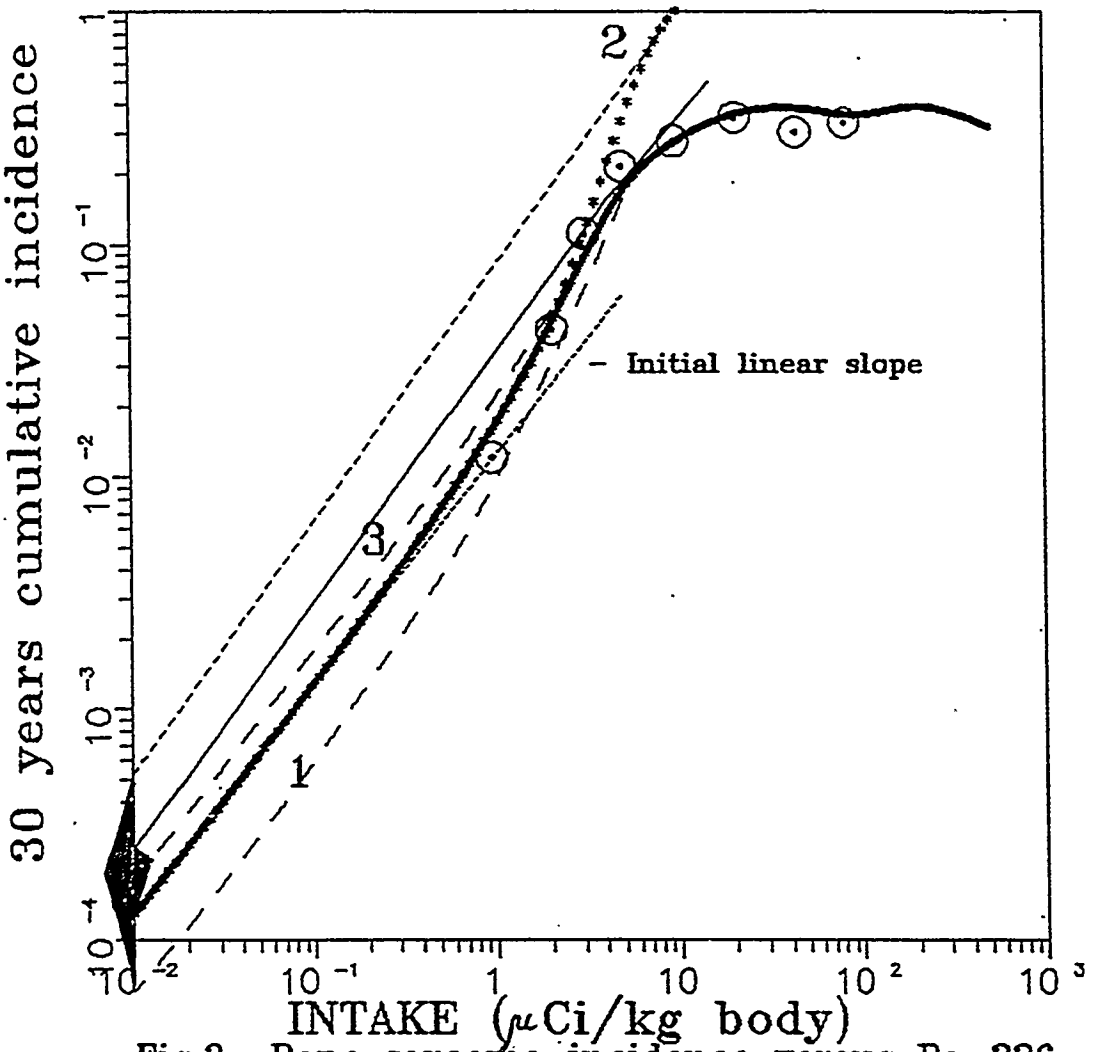


Fig.3 Bone sarcoma incidence versus Ra–226 single injection.

1 – model curve with parameters Bo=0.3 and C= 0.093 (maximum likelihood estimates).

2 – model curve not considering the role of initiated cells inactivation.

3 – Linear model.

– The length at this section is the most probable LEOF value (Linear Extrapolation Overestimation Factor.

– theoretically predicted maximum possible LEOF value.

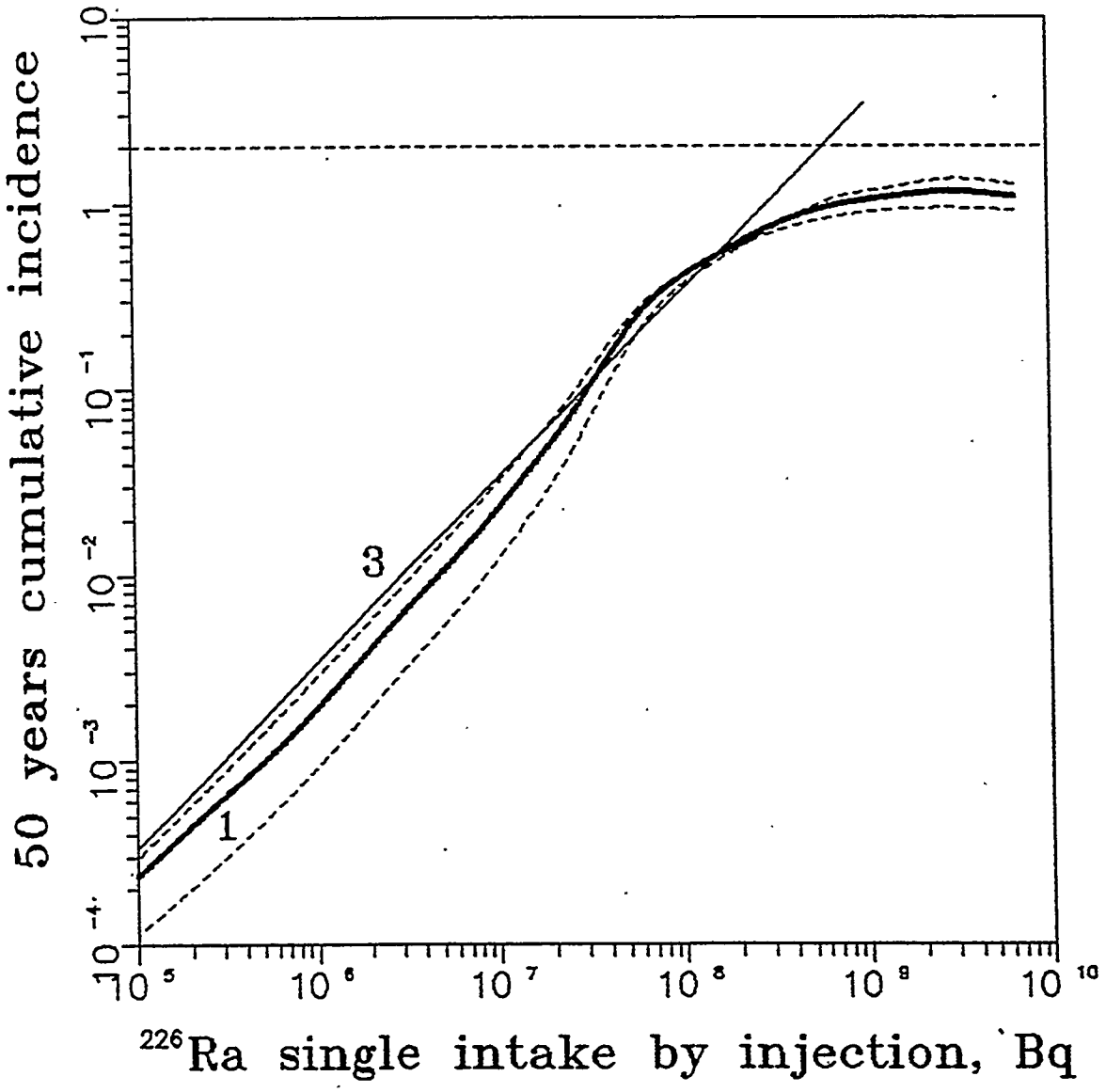


Fig. 4 Bone sarcoma incidence versus Ra-226 single injection.
1 - model curve with parameters Bo=0.3 and C= 0.093 (maximum likelihood estimates).
Dashed lines are model curves with upper and low bounds of parameter values Bo and C corresponding to 70% confidence area.
3 - Linear model (the line slope 3.4e-09 Bq^{-1}).

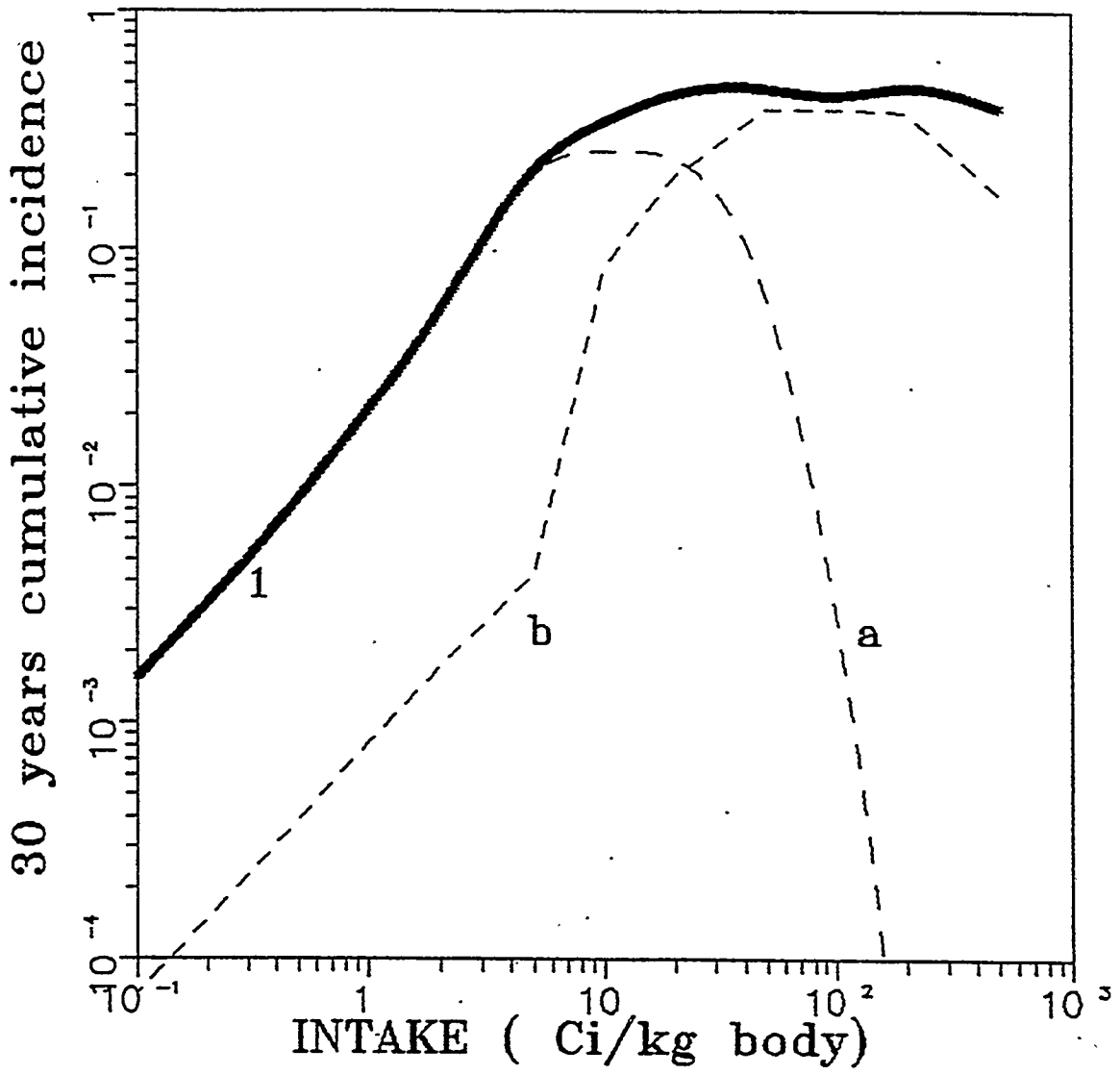


Fig.5 Bone sarcoma incidence versus Ra–226 single intake.
1 – model curve with parameters Bo=0.3 and C= 0.093 (maximum likelihood estimates).
a and b is a contribution to the total yield (curve 1) due to endosteal cells and marrow osteogenic cells exposure to alpha particles, respectively.

CURRENT STATUS OF ASSIGNMENT OF THE RISK FOLLOWING ALPHA-RADIOACTIVE NUCLIDES INJECTION

EPIDEMIOLOGICAL BASE : Ra-226 + Ra-228 HUMAN DATA

EXTRAPOLATION TO LOW DOSE: Linear ICPR-UNSCEAR model

VALUE OF THE RISK COEFFICIENT: Upper estimation of ICRP Publication 26 is 1.0 10-2 per Gy at endosteal surface. Truth value may be much LOWER.

To reduce the uncertainties at the risk assessement one needs a THEORY of the osteosarcomas induction by alpha emitters resulting in mathematical model of dose-response relationship.

THIS PRESENTATION IS AIMED AT:

1. To describe the worked out [IN GENERAL THEORY].
2. To discuss possible application of mathematical model of dose-response relationship resulting from the theory to the risk assignment.

COMPARISON OF THEORETICAL BASES OF DOSE-RESPONSE MODELS

EFFECTS TAKEN INTO CONSIDERATION	MARSHALL AND GROER MODEL	OUR MODEL
INITIATION STAGE	TWO INITIATION EVENTS WELL SEPARATED IN TIME	SINGLE INITIATION EVENT
"EXO-PROMOTION" PROCESS	PROPORTIONAL TO THE NATURAL CELL DIVISION RATE	
AUTO-PROMOTION PROCESS	IS NOT TAKEN INTO CONSIDERATION	CELL DEATH-INDUCED COMPENSATORY HYPERPLASIA
TARGET CELLS	ENDOSTEAL CELLS	ENDOSTEAL CELLS AS WELL AS MARROW OSTEOGENIC CELLS
NORMAL AND CELL-DEATH INDUCED KINETICS OF TARGET CELLS POOLS	POPULATION OF TARGET CELLS IS NOT SELF-RENEWING. INACTIVATED ENDOSTEAL CELLS IMMEDIATELY ARE REPLACED BY MARROW OSTEOGENIC CELLS.	POPULATION OF TARGET CELLS IS SELF-RENEWING. THIS POOL IS REPLACED BY MARROW OSTEOGENIC CELLS ONLY ITS FOCAL DESTRUCTION.
INTERMIXING OF OSTEOGENIC CELLS	NO CONSIDERED	ACCOUNTED FOR

ASSUMPTIONS OF THE MODEL

THE MODEL INVOLVE 8 MAIN ASSUMPTIONS CONCERNING: 1) MECHANISM OF (RADIATION) CARCINOGENESIS; 2) TARGET CELLS AND ITS LOCATION IN BONE; 3) CELL AND TISSUE KINETICS IN BONE UNDER/WITHOUT IRRADIATION.

FOR THE CONSTRUCTION OF DOSE-RESPONSE RELATIONSHIP FOR CANCER WE CAN SELECT, BASING ON THE THEORETICAL GROUNDS, SEVERAL PRINCIPAL ASSUMPTIONS CONSISTENT WITH CURRENT KNOWLEDGE OF MECHANISM OF CARCINOGENESIS INDUCED RADIATION:

A S S U M P T I O N 1 : PREMALIGNANT GENETIC DAMAGE IN CELL INDUCED BY RADIATION RELATE TO A GROUP OF COMPLETED CELLULAR END POINTS.

A S S U M P T I O N 2 : INITIATED CELL PHENOTYPICALLY DOES NOT DIFFER FROM NORMAL CELL AND RETAIN ALL THEIR PROPERTIES.

A S S U M P T I O N 3 : AN INITIATED CELL IS CONVERTED TO A MALIGNANT CELL THROUGH PROLIFERATION PROCESS.

USUALLY AS CELLS AT RISK FOR INDUCTION OF OSTEOSARCOMAS OSTEOGENIC CELLS ARE CONSIDERED, PARTICULARLY THOSE LOCATED ON OR NEAR THE ENDOSTEAL SURFACE OF BONE . HOWEVER STROMAL (OSTEOGENIC) CELLS OF THE BONE MARROW ARE FOUND FREQUENTLY WITHIN THE RANGE OF ALPHA-PARTICLES AS ALSO. THEREFORE WE ASSUME THE ASSUMPTION 4.

A S S U M P T I O N 4 : CELL AT RISK FOR INDUCTION OF OSTEOSARCOMAS ARE ENDOSTEAL CELLS AND MARROW OSTEOGENIC CELLS AS WELL. THE LAST CELLS ARE UNIFORMLY DISTRIBUTED WITHIN THE MARROW CAVITY AND THEIR CONCENTRATION IS SUBSTANTIALLY LOWER THAN OF ENDOSTEAL CELLS.

FOR DISCRIPTION OF CELL KINETICS WE INTRODUCED THE FOLLOWING MAIN ASSUMPTIONS:

ASSUMPTION 5 : ENDOSTEAL AND MARROW OSTEOGENIC CELLS ARE STEM CELLS, WHICH ARE CAPABLE OF SELF-RENEWAL AND OF DIFFERENTIATION.

ASSUMPTION 6 : RADIATION-INACTIVATED STEM CELLS REMAIN IN THE STEM CELLS COMPARTMENT UNTIL ITS RECEIVE A SIGNAL TO DIVIDE.

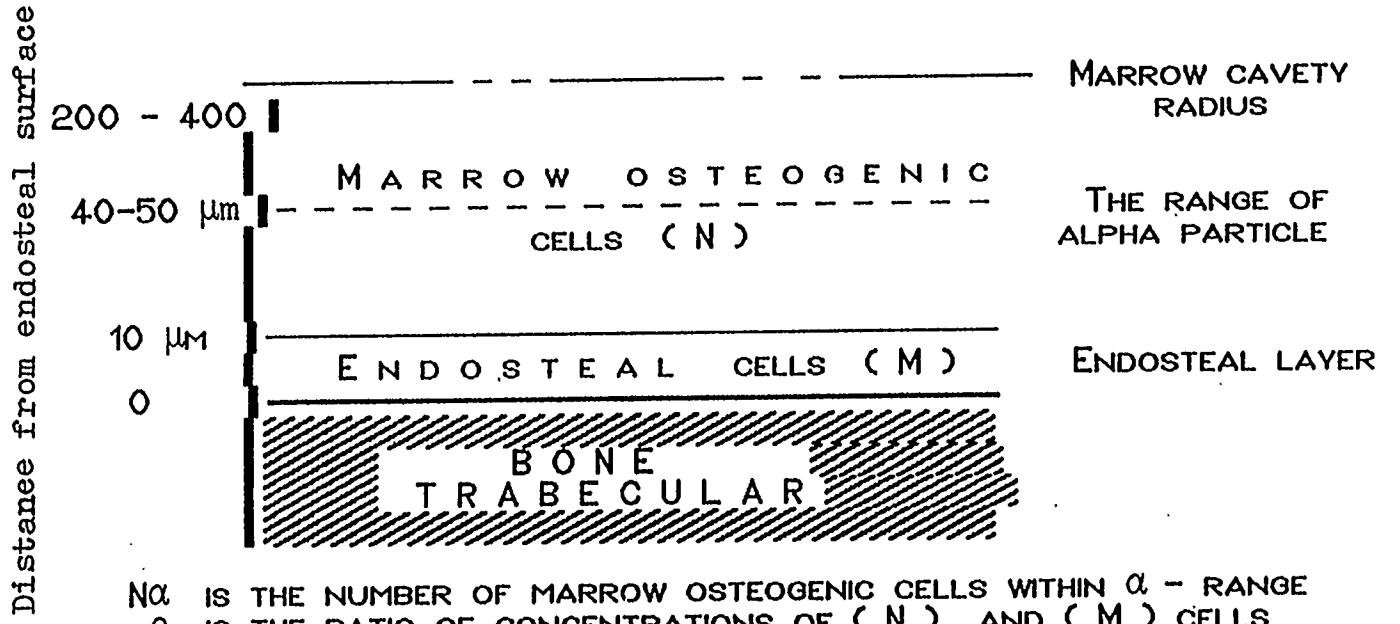
FOR ESTIMATION TO WHAT EXTEND AND THROUGH WHICH MECHANISM MARROW OSTEOGENIC CELLS MAY TAKE PART IN THE PROCESES OF BONE FORMATION WE INTRODUCED FOLLOWING ASSUMPTION:

ASSUMPTION 7 : MARROW OSTEOGENIC CELLS ARE THE RESERVE CELLS WHICH ARE RECRUTED TO BONE FORMATION ONLY AFTER COMPLETE INACTIVATION OF ENDOSTEAL CELLS.

AT LAST, WE INTRODUCED AN ASSUMPTION THAT OSTEOGENIC CELLS ARE MIXED IN BONE DUE TO ITS REMODELING.

ASSUMPTION 8 : PROCESSES OF SKELETAL REMODELING (BONE FORMATION AND RESORPTION) LEAD TO (GRADUATE) INTERMIXING OF ENDOSTEAL CELLS WITH MARROW OSTEOGENIC CELLS.

OSTEOGENIC CELLS IN BONE
(TARGET CELLS)



Nα IS THE NUMBER OF MARROW OSTEOGENIC CELLS WITHIN α - RANGE
ρ IS THE RATIO OF CONCENTRATIONS OF (N) AND (M) CELLS

FOR ρ = 0.1 N/M = 1500 g/ 60g * 0.1 = 2.5 .

Nα = V (Rα) / V (200 µm) * N = 0.2 N .

M + N = 3.5 M

Nα = 0.5 M

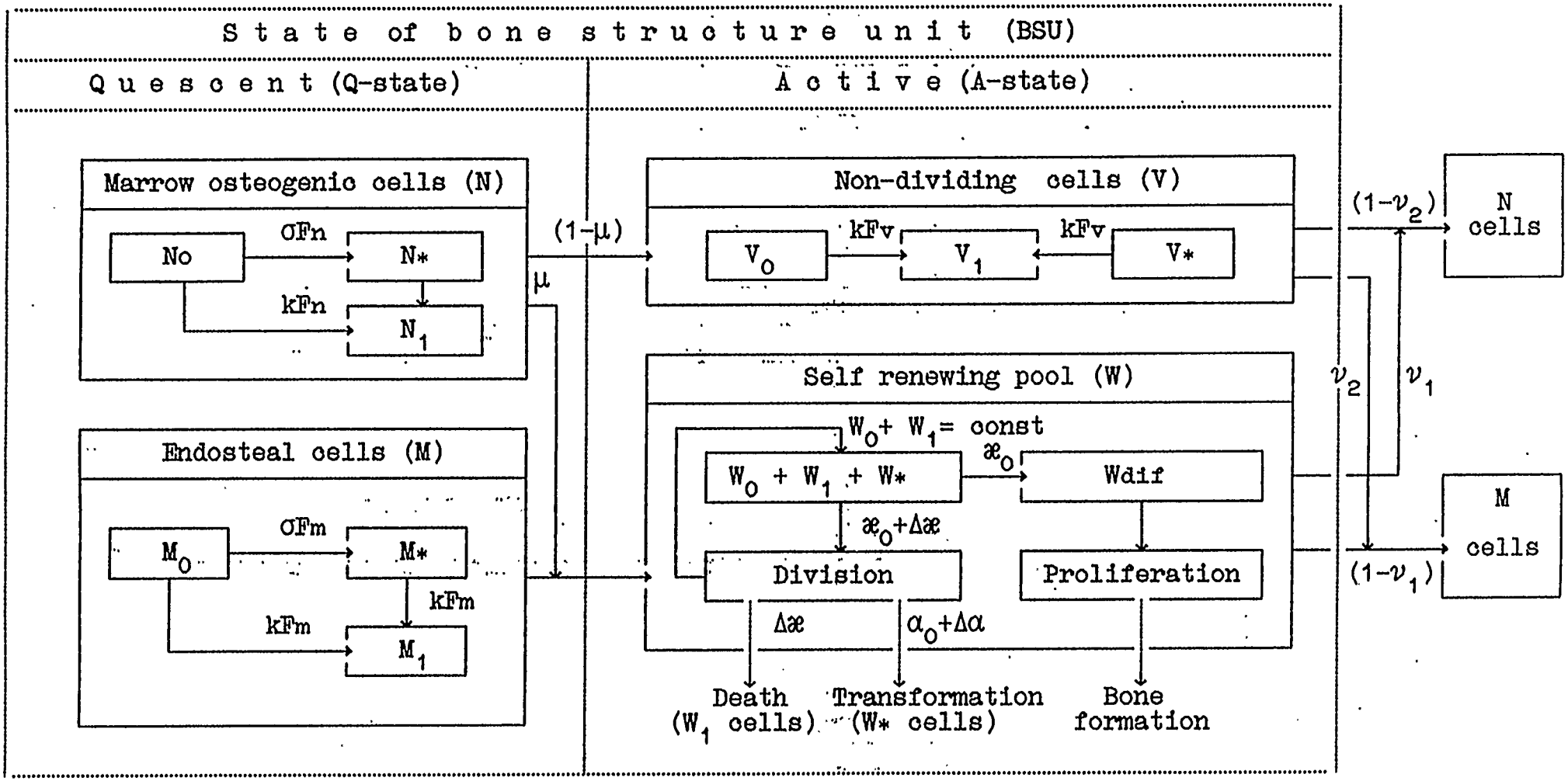


Fig.1. Funotional scheme of bone sarcoma induction by alpha emitters.

MATHEMATICAL FORMULATION OF THE MODEL
(THE MAIN EQUATIONS)

CUMULATIVE INCIDENCE OF OSTEOSARCOMAS

$$I(T+G) = C \sum_{N=1}^{M} W^*(TN+1) * LN \quad , M = [\, T / (To+TA) \,] \qquad (1)$$

W*(TN) IS THE NUMBER OF INITIATED CELLS AT THE BEGINNING OF A BONE FORMATION INTERVAL.

LN IS THE MEAN NUMBER OF OSTEOGENIC CELLS DIVISION DURING OF ONE CYCLE OF BONE FORMATION.

M IS THE NUMBER OF CYCLE (A-STATE) IN TIME T AFTER STARTING INTAKE RA.

1. THE NUMBER OF OSTEOGENIC CELL DIVISION DURING A-STATE

$$L = Lo + L(ind) = Lo + [\, Wo(To+TA) - Wo(To) * EXP(-.KFTo)] /S \qquad (2)$$

Lo IS THE PHYSIOLOGICAL NORMAL NUMBER OF OSTEOGENIC CELL DIVISION DURING OF ONE CYCLE OF REMODELING BONE SURFACE .

L(ind) IS THE NUMBER OF CELL DIVISION DUE TO CELL DEATH-INDUCED COMPENSATORY HYPERPLASIA.

Wo(To) IS THE NUMBER OF INTACT CELLS AT BIGINING A-STATE, WHEREAS Wo(To+TA) IS ONES AT END A-STATE.

S IS THE TOTAL NUMBER OF INTACT CELLS DURING A-STATE.

EXP(-KFTo) IS THE FRACTION OF NORMAL CELLS WHICH SURVIVE Q-STATE.

2. THE NUMBER OF INTACT (Wo), INACTIVATED (W1), INITIATED CELLS (W*) IN POPULATION OSTEOGENIC CELLS.

THIS CHARACTERISTICS ARE CALCULATED BY SOLVING A SYSTEMS DIFFERENTIAL EQUATIONS DISCRIBIED OSTEOGENIC CELL KINETICS DURING A- AND Q STATES.

MODEL PARAMETERS

1. THEORETICAL PARAMETERS

THEY MAY BE ESTIMATED ON THE BASIS OF AVAILABLE BIOLOGICAL DATA.

F	TIME SPECIFIC DOSE RATE OF α-RADIATION AT CELL AS FUNCTION OF RA INTAKE.
K	THE KILLING PROBABILITY OF α-IRRADIATION PER GY (K = 1.7 GY-1).
G	THE TIME PERIOD FOR TUMOR GROWTH (G = 5 YEARS).
TC	THE MEAN INTERVAL BETWEEN PERIODS OF BONE SURFACE REMODELING (TC = 2 YEARS).
TA	THE BONE FORMATION INTERVAL (TA = 60 DAYS).
Q	THE RATIO OF CONCENTRATIONS OF OSTEOGENIC CELLS IN BONE MARROW AND ENDOSTEAL LAYER (Q = 0.1).

THE MODEL INCLUDE ALSO 6 THEORETICAL PARAMERERS WITH HAVE NO CRITICAL INFLUENCE ON THAT PECULIARITIES OF DOSE-RESPONSE CURVE PREDETERMINING ITS EXTRAPOLATION PROPERTES.

2. FREE PARAMETERS

THEY ARE DERIVED BY MODEL FITTING TO EPIDEMIOLOGICAL DATA THROUGH MAXIMUM LIKELIHOOD ESTIMATION.

C	CONSTANT OF THE SCALING TYPE.
Bo	IT PREDETERMINES THE DEGREE OF NON-LINEARITY OF THEORETICAL DOSE-RESPONSE CURVE. WITHIN THE THEORY Bo VALUE IS CHARACTERISTIC TO DIVISION RATE OF OSTEOGENIC CELLS.

THE EQUATION FOR MODEL CURVE NOT CONSIDERING THE ROLE OF INITIATED CELL INACTIVATION

In this case non-linearity of the curve of interest results from auto-promotion only. The "artificial" curves can be described as

$$I = C F \{ Bo + [1 - \exp(-kFTo)] / S \} . \qquad (1)$$

Bo is free model parameter which within the theory is characteritic of cell division rate.
Wo, S is the number of intact osteogenic cells of self-renewing pool
S is the total number of osteogenic cell of self-renewing pool.
exp(-kFTo) is the fraction of cells which survive during Q-state.

For lowest intake $I = C F Lo$, while for relatively high intake ($kFTo > 1-2$) $Wo = S$ and therefore $I = C F (Lo + 1)$.

THEORETICALLY PREDICTED MAXIMUM POSSIBLE LEOF VALUE (LEOF - Linear Extarpolation Overestimation Factor)

Accoding to equation for "artificial" LEOF value equal

$$LEOF = I \text{ (high intake)} / I \text{ (low intake)} = (Bo + 1) / Bo$$

For $Bo = 0.3$ (0.1-0.7) we find that $LEOF = 4$ (2.5-11).
Uncertainty in estimation of LEOF value associated with Bo evaluation on epidemiological data.

LUNG AND SKELETON MALIGNANT TUMOR INDUCTION DUE TO HIGH LET EMITTERS

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The environment is constantly being supplied with transuranium elements. As a result of nuclear tests, more than 4 tons of plutonium, including 2.5 tons of ^{239}Pu, have been scattered throughout the world. By the end of 1978, the world nuclear-power industry had produced 77 tons of plutonium, 1 ton of americium, 4.5 tons of neptunium, and 260 kg of curium, partially released into the environment. Transuranium elements have become an integral part of surroundings and, in trace amounts, are found in human bodies in various parts of the world /1/. Working with these elements also results in their intake into the body and, in some cases, at levels dangerous for human health /2-4/.

Experimental studies show that malignant tumor induction is of primary importance in regard to the biological action of transuranium elements on the animal body. This effect can be observed over a wide range of absorbed doses, including those set as dose limits for workers and lower/5-8/. The information obtained has greatly influenced the philosophy of regulation of ionizing radiation. The threshold concept is known to have been substituted by a non-threshold one for stochastic somatic and genetic effects. A basic assumption of this concept is that "there is, within the range of exposure conditions usually encountered in radiation work, a linear relationship without threshold between dose and the probability of an effect" /9/. Clarification of quantitative relationship between these parameters for low-level radiation is a problem to be solved by health physics /10/.

This report aims at analysis of the dose-response relationship following rat exposure to ^{239}Pu, ^{241}Am, and ^{237}Np over a wide range of doses, and also at comparison between risk fact obtained experimentally and those recommended by the ICRP /9/. The biological effect of transuranium

elements was investigated regarding malignant tumor incidence in rat bone for all the pathways of intake covered and in the lung (cancer, adenocarcinoma, hemangiosarcoma) for intakes of radionuclides into the respiratory system. The choice of these criteria is due to the fact that lung and skeleton malignant tumors are constantly revealed in damaged rats but are very rare in controls. In the analysis of lung malignant tumors animals with lymphoreticulosarcomas were left out of account, since their incidence in controls amounted to 10% /11/.

The data reported here have been collected during more than 20 years of research. The effects of ^{239}Pu, ^{241}Am, and ^{237}Np were studied following inhalation, intratracheal, intraperitoneal, and hypodermic incorporation of soluble and relatively soluble compounds (citrate, nitrate, oxalate, ammonium plutoniumpentacarbonate dissolved in excess of carbonate or in water, hydrolysis products of fluorine-containing compounds of plutonium). Absorbed doses to the lung and skeleton were estimated using radiometric data on these organs and concentration patterns obtained in similar experiments. Animals were all subjected to autopsy; preparations for the histologic analysis were made by conventional methods. In most cases, autopsy was preceded by skeleton X-raying to reveal osteosarcomas. Animals were divided into groups according to integral absorbed doses, each group comprising animals from different experiments with doses differing no more than by a factor of two. Average dose within a group as well as tumor incidence were estimated taking into account mean dose and the number of animals. A 95% confidence interval was evaluated according to Fisher criterion with correction for small samples /12/. The results were treated using the least squares method for linear sections of the curves on a log-log scale.

Table 1 gives generalized data on the carcinogenic effect of transuranium elements on the rat lung. It follows that lung malignant tumor incidence grows from 1. 7 to 8% within the dose range not resulting in life shortening (24.8 to 234 cGy), with spontaneous incidence of 0.4% in controls. Over this dose range, the dose-response relationship can be expressed as $P(\%) = 0.195D^{0.677}$. The equation for excess tumor incidence (minus spontaneous level) is $P(\%) = 0.094D^{0.809}$. For this dose range, the equations do not suggest a directly proportional relationship between lung malignant tumor incidence and dose, which is confirmed by tumor incidence per a dose unit. At doses causing life shortening (234 to 435 cGy), the effect is disproportionate to dose, increasing from 8 to 21.4%. Further dose increase brings about a decrease of malignant tumor incidence in a group and per a dose unit, with life shortening continued.

It should be noted that the dose-response curve obtained is true for a heterogeneous population, regarding both the time of experiments and means of radionuclide administration (inhalation, intratracheal incorporation). This complicated relationship manifests itself most distinctly following intakes of transuranium elements by inhalation. In this case, at doses above 600 cGy, there is a certain relationship between tumor incidence and the nature of a radionuclide, e.g. tumor incidence proves to be higher for plutonium than for americium. At doses producing no life shortening, these differences are either leveled or inconsistent. It is noteworthy that in groups of rats with absorbed doses to the lung from 0.075 to 8 cGy malignant lung tumors also occurred, though showing no consistent pattern. However, the evidence is insufficient (15 rats with tumors out of 918 animals) for any conclusion to be drawn.

It should be stressed that malignant lung tumors develop, with different probabilities, over a wide range of doses, including those adopted by the USSR Standards of Radiation Protection (SRP-76) as permissible. The results of many years do not indicate any threshold for the effect of transuranium elements concerning lung malignant tumor induction. At the same time, the shape of the curve is evidently affected by the immunological status. One may assume that activation of the immunological surveillance system determines the shape of the curve, with an exponent less than 1, for doses from 24.8 to 234 cGy, while deficiency of this system results in a disproportionate increase of tumor incidence at 435 cGy.

In Table 2, data is listed on the blastomogenic effect of transuranium elements on the rat skeleton. It results from the data presented that osteosarcoma incidence (0.68 to 2.9%) increases, in fact, directly proportional to dose within the range of 5.2 to 29.7 cGy; and for a wider range (5.2 to 218 it is described by the equation $P(\%) = 0.192D^{0.781}$. With further dose increase, almost 8-fold (up to 1860 cGy), osteosarcoma incidence grows 2-fold only (up to 22.5%), tumor incidence per a dose unit falling by a factor of 5. One may agree that the latter fact results from the anticarcinogenic effect of high doses of α-radiation on bone surfaces, as well as from life shortening limiting the carcinogenic effect realization /8/. It should be pointed out that recent experiments /13/ with inhaled or percutaneously (through abrasions and pricked wounds) incorporated ^{239}Pu gave similar osteosarcoma incidence per 1 cGy for 5 to 1020 cGy, indicating a directly proportional relationship. The above evidence, to a greater degree than the lung data, demonstrates a linear non-threshold dose-response relationship at low doses, which may be 8 factor of 2 or 3 higher or lower than those accepted as permissible (15

cGy over a working life of 50 years), in agreement with the new ICRP concept.

From considerations given and equations presented, risks of lung and skeleton malignant tumors have been calculated for 50 years of an occupational life at permissible exposure levels /14/. In Table 3, the possibility and percentage of (a) human mortality from spontaneous malignant tumors of the lung and skeleton; (b) tumors induced by transuranium elements in rata and extrapolated to man; (c) tumors in man estimated using the ICRP risk factors /9/; (d) mortality in safe industries are summarized. It follows that lung and skeleton tumor incidence in a person exposed for 50 years to maximum permissible doses (MPD) of 15 and 30 $cSv \cdot year^{-1}$ will be 1.8 and 1.5%, respectively, as estimated from experimental data on rats. These values are equal or compatible with 1.5 and 0.75% calculated with the help of the ICRP risk factors. Similar results obtained by two different methods of risk assessment imply similarity in rat and human sensitivity to transuranium elements for malignant tumors of the lung and skeleton, thus justifying direct extrapolation of results in the rat to man /6, 15/. Moreover, excess tumor incidence in man exceeds twice the spontaneous level for the lung and by a factor of 10 or 20 that for the skeleton. Mortality in this case grows 5-10 fold as compared with deaths due to other causes in radiation work or in safe industries. These estimates support the Soviet scientists' proposal to keep the average individual dose received by a controlled population at a 1/10 level of the appropriate worker dose limit. Provided this condition is met, an excess integral risk of fatal tumors mentioned will be only a small part of the spontaneous level. For reasons given, the linear non-threshold concept holds for the carcinogenic effect of transuranium elements.

The study involved 110 mongrel dogs, male and female, which survived the appearance of the first malignant tumor. At the beginning of the experiment, the animals were 2-4 years of age, with a mean weight of 15.8 ± 0.5 kg. The dogs were exposed to a single inhalation of one of the following aerosol compounds: polymeric $^{239}Pu(NO_3)$, pH 1.5-2, AMAD = 1 μm, 39 animals; $^{239}PuO_2$, AMAD = 0.065 μm, 15 animals; monomeric $^{241}Am(NO_3)_3$, pH 1.5-2, AMAD = 1 μm, 48 animals; HNO_3, pH = 1.5, control, 4 animals; H_2O, control,4 animals.

An average life-span of the control was 3885 ± 208 days and that of the exposed ranged from 27.1 to 138.8% of the control, depending on the radionuclide intake.

The incidence of dog malignancies was considered in relation to the initial radionuclide content of the organs of primary deposition, i.e. the lung, skeleton and body. In view of the radionuclide metabolic kinetics, organ doses were estimated, including the total dose and the daily dose rate to critical organs.

Followed up till the death of the last animal, the dogs developed 110 malignancies, including 52 lung cancers, 43 osteosarcomas, 8 primary liver cancers and single cases of rectal cancer, cancer of appendages of the skin, melanoma, adrenal cancer, thyroid cancer, prostate cancer, seminoma, and 27 benign tumors of different sites. The spectrum of tumors is wider, the more transferable the administered radionuclide.

In the dogs exposed to aerosol plutonium (Table 4) and americium (Table 5), a clear-cut relationship was observed between the time from the onset of lung cancer till the death and the amount of the radionuclide inhaled and the absorbed dose to the lung. Thus, the highest lung cancer incidence (8 out of 8) followed an intake of 2.9 ± 0.5 $kBq \cdot kg^{-1}$ at a dose rate of 2 ± 0.03 $mGy \cdot d^{-1}$ and a total dose of 548 ± 54 cGy, the life-span being 69% of the normal average one. As may be seen from Table 4, no lung cancer occurred at a dose of 40 ± 8 cGy and at an average dose rate of 0.12 ± 0.04 $mGy \cdot d^{-1}$ to the lung.

Doses of 287–1999 cGy and dose rates from 1.2 ± 0.4 to 12 ± 5 $mGy \cdot d^{-1}$ due to plutonium oxide with an AMAD of 0.065 μm induced lung cancer in 3–4 dogs out of 5. However, just as in the case of colloidal $^{239}Pu(NO_3)_4$, the time of the tumor development depends on the lung dose. Out of 8 control dogs, one case of lung cancer was observed shortly before the death.

Inhalation of ^{241}Am results in less lung cancers than that of plutonium, with absorbed doses to the lung being comparable. The reduction of a dose rate to the lung from 6.9 ± 1.2 to 0.16 ± 0.02 $mGy \cdot d^{-1}$ doubles the latent period, while tumor incidence amounts to 50% (4 out of 8). At higher dose rates, 3 out of 5 animals developed lung tumors. A relatively low incidence of lung cancer caused by $^{241}Am(NO_3)_3$ might reflect specific features of the dose microdistribution in the lung tissue. Lung malignancies included adenocarcinomas (65%), squamous cell carcinomas (15%), dimorphous cancers (15%) and undifferentiated cancers(5%).

Tables 6 and 7 give osteosarcoma incidence by the dose and dose rate to the skeleton following ^{239}Pu or ^{241}Am intake by inhalation. It may be seen

that skeleton tumors induced by polymeric $^{239}Pu(NO_3)_4$ are less frequent than those from ^{239}Pu O_2 with an AMAD of 0.065 μm which behaves like a soluble compound. Skeleton doses from incorporated plutonium ranged from 3.8 ± 0.3 to 484 ± 61 cGy and dose rates varied from 0.009 ± 0 0004 to 2.67 ± 1.1 mGy•d^{-1}, respectively. It is clearly seen that no osteosarcoma occurred at a skeletal dose rate of 0.07 ± 0.01 mGy•d^{-1} or lower, although the average life-span of these animals was even longer as compared with the controls.

Table 7 shows that americium inhalation results in rather high skeleton doses, causing osteosarcoma. Our experiments failed to demonstrate safe radiation levels. Osteosarcomas occurred at doses from 83 ± 19 to 2898 ± 381 cGy and at dose rates from 0 3 ± 0 08 to 22 ± 3 mGy• d^{-1}.

At doses from 620 ± 22 to 2898 ± 381 cGy, osteosarcoma incidence was 90-100%, while at doses of 295 ± 33 cGy and 83 ± 19 cGy, it was 50% and 25%, respectively (5 out of 10 and 2 out of 8 animals died from osteosarcoma). Dose rates were 0.9 mGy•d^{-1} and 0.3 mGy•d^{-1}. For 90–100% osteosarcoma incidence, the latent period made up 39.7–50.5% of the average life-span, and for 50% and 25% incidence, it was 82.4% and 65.2%, respectively.

Table 8 shows that the lowest doses to induce lung and skeleton malignancies are very similar and independent, in fact, of the type and physical and chemical conditions of the radionuclide inhaled. These doses to the lung and skeleton over the latent period were 34–86.8 cGy and 45.9–79.3 cGy, respectively, the corresponding dose rates ranging from 0.08 to 0.45 mGy•d^{-1}. Lower doses and dose rates to these organs induced no malignancy.

If cancer incidence following exposure to densely ionizing radiation is independent of the dose rate but depends on the total dose, one can empirically calculate safe dose rates for humans. These should be lower than safe levels for dogs by the same factor as the average human life-span is longer than that of the dog.

For the lowest carcinogenic impact of radionuclides, the dose rate must not exceed 0.08 mGy : 6 = 0.013 mGy•d^{-1} to the lung and 0.36 mGy : 6 = 0.06 mGy•d^{-1} to the skeleton. The safe levels should be reduced by an acceptable risk coefficient.

The incidence of lung cancer and osteosarcomas following inhalation of ^{237}Np, ^{239}Pu, ^{241}Am at amounts which do not affect the life span (Table

10), is also dependent on radiation dose to organ. The incidence of tumors per 1 Gy of the absorbed dose decreases with increasing total dose. It is likely that a portion of energy of alpha-radiation either is lost in the killed cells or induces irreversible cell damage.

There probably exist minimum-significant doses (Table 11) which are capable of inducing stochastic effects represented by malignant tumors of the lungs and skeleton in rats, dogs and humans. Lung carcinoma develops in rats and dogs after absorption of 0.6 and 6.8 Sv, respectively. Skeleton tumors in rats, dogs and humans occur due to the absorption of 0.6; 9.2 and 17 Sv. Species-specific differences are determined primarily by the differences in life spans. It should be noted that the annual dose rate for neoplasm induction ranges from 0.2 to 0.7 in these three mammals species.

Liver cancer (Table 12) shortens life span in dogs proportional to the amount of ^{241}Am inhaled. At "minimum" amounts of the radionclide, 2.6–4.6 $kBq \cdot kg^{-1}$, and doses to the liver of 0.32 and 1.43 Gy, the average daily dose rates amount to 0.4 ± 0.06 mGy or 8 mSv. This estimate is approaching the dose levels which are able to induce the development of lung cancer and osteosarcoma. In all likelihood the epithelial and connective tissues have a similar sensitivity to blastogenic effect of alpha-radiation.

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Table 1. Lung Malignant Tumor Incidence in Rats (Save for Lymphoreticulosarcoma) Following Intakes of Transuranium Elements into the Respiratory System

		Number of rats		Percent of rats with tumors			
Dose range, cGy	Average dose to lung, cGy	total	with tumors	total	confidence interval	per 1 cGy	Average lifetime % of control
Control	0	532	2	0.4	0 - 0.9	0	10 ± 2.3
21–40	24.8	542	9	1.66	0.8 - 3.0	0.067	98.5 ± 2.4
41–80	60.7	797	27	3.39	2.4 - 4.4	0.056	99.1 ± 3.3
81–160	117	665	30	4.51	3.9 - 6.3	0.039	95.8 ± 1.8
161–320	234	673	54	8.02	6.0 - 10.2	0.034	96.8 ± 2.0
321–640	435	878	188	21.4	18.7 - 24.2	0.049	93.1 ± 2.0
641–1280	914	1215	299	24.6	22.5 - 27.1	0.027	76.7 ± 2.8
1281–2560	1516	597	108	18.1	15.4 - 21.4	0.012	55.9 ± 6.2

Table 2. Osteosarcoma Incidence in Rats Following Intakes of Transuranium Elements by Different Pathways

		Number of rats		Percent of rats with tumors			
Dose range, cGy	Average dose to lung cGy	total	with tumors	total	confidence interval	per 1 cGy	Average lifetime % of control
Control	0	1520	0	0	–	0	100
1– 10	5.2	1616	11	0.68	0.3 - 1.1	0.13	97.2 ± 1.7
11– 20	13.6	1008	13	1.30	0.7 - 2.1	0.096	99.0 ± 2.0
21– 40	29.7	902	26	2.90	1.9 - 4.1	0.12	95.3 ± 1.7
41– 80	61.2	1499	49	3.27	2.4 - 4.2	0.054	93.3 ± 3.4
81– 160	120	927	68	7.30	5.7 - 9.1	0.061	88.7 ± 3.8
161– 320	218	877	103	11.7	9.6 - 13.9	0.054	78.5 ± 6.0
3211– 640	430	1832	251	13.7	12.1 - 15.3	0.032	72.6 ± 4.0
641–1280	844	1114	225	20.2	17.8 - 22.7	0.024	70.5 ± 5.0
1281–2560	1860	372	84	22.5	18.3 - 27.0	0.012	53.7 ± 5.0

Table 3. Mortality From Lung and Skeleton Malignant Tumors Estimated According to Experimental and Epidemiological Data

Effect, condition	Possibiltity in year	Cases per 10^6 persons in year	in 50 years	Percent in 50 years
Excess tumors				
lung, 15 cSv • $year^{-1}$	$3.6 \cdot 10^{-4}$	360	18000	1.8
skeleton, 30 cSv •$year^{-1}$	3.0 • 10-4	300	15000	1.5
(according to experimental data)				
Excess tumors				
lung, MPD = 15 cSv • $year^{-1}$	$3.0 \cdot 10^{-4}$	300	15000	1.5
skeleton, MPD = 30 cSv • $year^{-1}$	$1.5 \cdot 10^{-4}$	150	7500	0.75
(according to ICRP Publ. 26)				
Spontaneous tumors				
lung	$2.5 \cdot 10^{-4}$	250	12500	1.25
skeleton	$1.4 \cdot 10^{-5}$	14	700	0.07
Mortality due to other causes				
in radiation work				
or in safe industries	(0.5-1) • 10^{-4}	50–100	2500–5000	0.25–0.5

Table 4. Dog Lung Cancer After ^{239}Pu Inhalation

Compound	No. of Dogs	No. of Tumors	kBq • kg^{-1}	Average life span, percentage control	Lung dose, cGy	
					Total	per day
^{239}Pu	8	6	11.6 ± 1.1	32.1 ± 1.7	3914 ± 343	3.16 ± 0.39
pH • 1.5	8	7	5.9 ± 1.3	52.5 ± 8.4	1592 ± 179	0.786 ± 0.25
Polymeric	8	8	2.9 ± 0.5	69.2 ± 6.2	548 ± 54	0.205 ± 0.03
^{239}Pu $(NO_3)_4$	8	7	1.9 ± 0.5	86.6 ± 12.1	176 ± 28	0.063 ± 0.008
pH = 1.5 AMAD = 1 µkm	7	0	0.8 ± 0.4	87.3 ± 11.6	40 ± 8	0.012 ± 0.004
239Pu	5	3	13.5 ± 4.4	47.4 ± 12.1	1999 ± 264	1.20 ± 0.5
$239PuO_2$	5	4	11.5 ± 3.3	45.6 ± 7.7	1120 ± 134	0.61 ± 0.19
AMAD = 0.065 µkm	5	3	8.6 ± 3.3	61.4 ± 10	287 ± 69	0.12 ± 0.04
Intact Control	4	0	0	100% = 3835 ± 477	0	0
HNO_3, pH 1.5	4	1	0	3885 ± 202	0	0
Control inhalation of NHO_3, pH = 1.5 AMAD = 1 µkm						

Table 5. Dog Lung Cancer After Inhalation of Monomeric $^{241}Am(No_3)_3$

No. of Dogs	No. of Tumors	kBq • kg^{-1}	Average life span, percentage control	cGy per lung	cGy per day
5	0	19.8±2.9	36.0±2.3	2440±197	1.76 ±0.40
5	3	14.5±4.6	48.5±9.6	1295± 60	0.69 ±0.12
10	3	8.1±0.8	46.4±9.2	733± 59	0.41 ±0.06
10	1	8.5±1.1	55.7±6.7	349± 20	0.16 ±0.02
10	2	6.7±1.2	63.1±9.5	169± 21	0.079±0.02
8	4	1.7±0.7	84.0±7.6	51± 3	0.016±0.002
8	1	0	100%-3835±477		
Control			3885±208		

Table 6. Dog Osteosarcomas After ^{239}Pu Inhalation

Compound	No. of Dogs	No. of Tumors	$kBq \cdot kg^{-1}$	Average life span, percentage control	Skeleton dose cGy	Skeleton dose cGy/day
	8	0	7.0±1.2	52.3± 7.8	208 ±34	0.103 ±0.01
Polymeric	8	1	7.2±1.7	46.5± 6.7	126 ± 5	0.07 ±0.01
$Pu^{239}(NO_3)4$,	8	2	6.4±1.5	39.9± 3.4	78 ± 3	0.05 ±0.006
pH=1.5	8	0	1.0±0.2	90.9± 6.8	23.6± 6	0.007 ±0.001
	7	0	0.3±0.1	109± 8.0	3.8± 0.3	0.0009±0.00004
$^{239}PuO_2$	5	3	13.8±3.7	47.0± 9.8	484 ±61	0.267 ±0.11
AMADf -	5	2	12.2±4.0	45.6±11.7	233 ±27	0.132 ±0.05
0.065µm	5	1	8.1±3.3	59.3±10.9	88 ±15	0.038 ±0.01
Intact control	4	0	0	1004-3835±477	0	0
Control inhalation HNO_3: pH=1.5	4	0	0	3885±208	0	0

Table 7. Dog Osteosarcomas After Inhalation of Monomeric Am^{241} $(NO_3)_3$

No. of Dogs	No. of Tumors	$kBq \cdot kg^{-1}$	Average life span, percentage control	cGy per skeleton	cGy perday
5	4	20.7±4.5	39.7±3.7	2898±381	2.2 ±0.3
5	5	12.1±2.0	40.4±4.2	1142±141	0.93±0.09
10	9	10.0±2.3	46.5±6.3	900± 24	0.50±0.04
10	9	9.2±1.7	50.5±7.2	620± 22	0.32±0.03
10	5	3.5±1.6	82.4±6.7	295± 33	0.09±0.008
8	2	3.3±0.9	65.2±9.0	83± 19	0.03±0.008
Control	0	0	3835±477	0	0
		0	3835±208		

Table 8. The Lowest Doses to the Dog Organs for Malignancies Observed

Malignanacy	Compound	$kBq \cdot kg^{-1}$ of body weight	Average life-span, Percentage of control	Dose, cGy	
				Total	Per Day
	$^{239}Pu(NO_3)_4$	0.16	138.3	81.9	0.015
Lung cancer	$^{239}PuO_2$ [0.065 μm]	0.48	93.9	86.8	0.024
	$^{241}Am(NO_3)_3$	0.63	104.4	34.0	0.008
Osteosarcoma	$^{239}Pu(NO_3)_4$	4.1	38.5	68.2	0.045
	$^{239}PuO_2$ [0.065 μm]	5.4	56.8	79.3	0.036
	$^{241}Am(NO_3)_3$	8.6	27.1	45.9	0.043

Table 9. Morphological Cancer Pattern in Dogs After Inhalation of Transuranic Elements

Compound	$^{239}Pu(NO_3)_4$	$^{239}PuO_2$	$^{241}Am(NO_3)_3$	Total	Control
Number of Animals	39	15	48	102	8
Lung adenocarcinoma	18	6	11	35	1
Lung squamous cell carcinoma	6	0	2	8	0
Undifferentiated cancer	1	0	0	1	0
Lung dimorphous cancer	4	4	1	9	0
Osteosarcoma	3	6	36	45	0
Liver cancer	0	1	7	8	0
Rectal cancer	1	0	0	1	0
Skin cancer	1	0	1[x]	2	0
Thyroid cancer	0	0	2	2	0
Adrenal cancer	0	1	0	1	0
Seminoma	0	0	0	0	1
Prostate cancer	0	0	1	1	0
Total tumors	34	18	61	113	2
Tumors per animal	0.87	1.20	1.27	1.11	0.25
x - Melanoma					

Table 10. Lung Cancer and Osteosarcoma Incidence Among Rats at ^{237}Np, ^{239}Pu, ^{241}Am Intake Without the Average Lifetime Shortening

Lungs				Skeleton			
cGy	No. of Rats	No. of Tumors	Per 1 cGy	cGy	No. of Rats	No. of Tumors	Per 1 cGy
4	329	8	0.600	8	1515	11	0.090
31	691	36	0.167	33	998	21	0.063
92	1113	35	0.034	64	917	22	0.037
224	580	48	0.037	382	976	107	0.029

Table 11. Stochastic Effects Due to Minimum Internal Doses

Nuclide	Disease	Studied Object	Gy	Sv
^{239}Pu	Lung Cancer	Rat	0.03–0.05	0.6–1
	Lung Cancer	Dog	0.34–0.86	6.8–17.2
^{241}Am	Osteosarcoma	Rat	0.03–0.05	0.6–1
	Osteosarcoma	Dog	0.46–0.79	9.2–15.8
^{226}Ra	Osteosarcoma	Human	0.85	17

Table 12. Carcinoma of the Dog Liver After ^{241}Am inhalation

	Percent Average	Dose, cGy	
kBq • kg^{-1}	Lifetime	Total	Per Day
18.7 ± 3.6	53.3 ±15.0	2399 ± 162	1.17 ± 0.35
10.9 ± 2.0	36.2 ± 4.9	1590 ± 113	1.14 ± 0.13
11.1 ± 2.4	42.6 ± 4.9	1055 ± 45	0.64 ± 0.05
9.6 ± 1.8	48.7 ± 3.4	596 ± 19	0.32 ± 0.02
4.6 ± 1.6	73.0 ± 8.8	320 ± 22	0.04 ± 0.006
2.6 ± 0.8	81.6 ± 5.7	143 ± 22	0.04 ± 0.006

Table 12. Carcinoma of the Dog Liver After ^{241}Am inhalation

	Percent Average	Dose, cGy	
kBq • kg^{-1}	Lifetime	Total	Per Day
18.7 ± 3.6	53.3 ±15.0	2399 ± 162	1.17 ± 0.35
10.9 ± 2.0	36.2 ± 4.9	1590 ± 113	1.14 ± 0.13
11.1 ± 2.4	42.6 ± 4.9	1055 ± 45	0.64 ± 0.05
9.6 ± 1.8	48.7 ± 3.4	596 ± 19	0.32 ± 0.02
4.6 ± 1.6	73.0 ± 8.8	320 ± 22	0.04 ± 0.006
2.6 ± 0.8	81.6 ± 5.7	143 ± 22	0.04 ± 0.006

Table 13. Parameters of ^{241}Am Extraction From the Organs After Inhalation

Organ	Species	Fraction	T-day	Fraction	T-day
Lungs	Rat	0.050	7	0.03	170
	Dog	0.42	18	0.10	625
Skeleton	Rat	-	-	0.20	2000
	Dog	-	-	0.50	9900

Table 14. Carcinoma of the Dog Liver After ^{241}Am Inhalation

$kBq \cdot kg^{-1}$	Average Lifetime	Dose, cGy	
18.7±3.6	53.3±15.0	2399±162	1.17±0.35
10.9±2.0	36.2± 4.9	1590±113	1.14±0.13
11.1±2.4	42.6± 4.9	1055± 45	0.64±0.05
9.6±1.8	48.7± 3.4	596± 19	0.32±0.02
4.6±1.6	73.0± 8.8	320± 22	0.04±0.006
2.6±0.8	81.6± 5.7	143± 22	0.04±0.006

Table 15. Absorption for 50 Days After Inhalation. %

$Pu(NO_3)_4$ Polymer	$(NH_4)_6Pu(CO_3)_5$ Pentacarbonate	$Pu(NO_3)_4$ Monomer	Chloride Pu(III), Pu(IV) Np(V) Chloride, Citrate, Acetate, Oxalate	Chloride Am(III) Citrate Nitrate	Chloride Np(V-VI) Nitrate
6	9	12	23-35	60	70

A Theoretical Concept of Low Level/Low LET Radiation Carcinogenic Risk (LLCR) Projection

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INTRODUCTION

Carcinogenic risk to humans resulting from low level/low LET radiation exposure (LLCR) has not been observed directly, because epidemiological observations have not yet provided statistically significant data on risk values. However, these values are of great interest for radiation health science and radiation protection practice under both normal conditions and emergency situations. This necessitates the development of an acceptable method of LLCR projection which includes, specifically, transferring the risk patterns from "epidemiologically measured" ones, at high doses and/or dose rates, to the "prognostically evaluated" ones, for low level radiation.

Conceptual differences exist between "measured" and predicted or "prognostical" risk coefficients. The former result from scientific investigations, accompanied with all the reservations and uncertainties inherent to them. The latter possess absolutely unscientific features such as unreserved precision, groundless details and immense universality. However, the differences between these coeffiecients are not paradoxical.

Prognostic risk coefficients are meant to ensure LLCR projection for practical purposes. LLCR projection acts as a quantitative measure of the hazards of exposure situations, and must not be influenced by the controversies of current knowledge, so that any individual dealing with LLCR projections could keep them "out of brackets". The important feature, however, of any step to derive the "prognostic" risk coefficients from "measured" ones is its persuasiveness with experts and decision makers in the areas of application of LLCR patterns; ie, setting radiation standards, substantiating intervention levels, and appreciating exposed cohorts, whether they are epidemiologically valuable or not.

This report presents a theoretical contribution to the validation of dose and dose rate efficiency factors (DDREF) transforming carcinogenic risk coefficients from those revealed in A-bomb survivors to factors appropriate for the projection of the risk resulting from very low levels of low LET radiation.

1. THE CHOICE OF AN ACCEPTABLE THEORY.

"Every theory is worth each other one" I. Goethe. "Faust" .

DDREF validation involves overcoming the lack of direct epidemiological evidence at low doses. This requires the formulation of a mathematical model of dose-response relationship for its quantitative extrapolation to this dose range. To compensate for the lack of epidemiological evidence, an appropriate mathematical model supports this procedure with some additional information relevant to the risk extrapolation beyond formal mathematical treatment of the observed data. Does any mathematical model possess this property? It depends entirely on the principles of the model construction.

As an example, let us examine the linear-quadratic model F(D) commonly used [1] in carcinogenic risk extrapolation:

$$F(D) = (\alpha D + \beta D^2) \bullet \exp[-aD - bD^2], \text{ where}$$

D is the dose of irradiation;terms $(\alpha D + bD^2)$ and $\exp[-aD - bD^2]$ are to take into account the effect of cancer initiation and inactivation of initiated cells due to the same irradiation event, respectively.

This equation fails to fit any observed dose-response relation for radiation-induced cancer i.e., "theoretical" values of parameters $\{\alpha,\beta,a,b\}$ are used which result from independent evidence, for example, data of cell radiobiology. Moreover, the dose-response relationship for radiation leukogenesis in mice has considerable influence of cell inactivation, but this process causes almost no traceable effects in humans. This controversy cannot be explained mechanistically by the linear-quadratic model. We should agree that no implied mechanisms of radiation carcinogenesis are actually intrinsic to the terms of this equation. The type of the parameter set $\{\alpha,\beta,a,b\}$ confirms that all of these parameters are

free, and their values are adjusted respectively throughout the model, applied to points of a particular epidemiological observation scattered broadly along the "dose-effect" graph.

In respect to this, the linear-quadratic equation becomes an "empirical ad hoc" model, with its general construction predetermined primarily by the behavior of a dose dependency obtained as a result of an individual study. Therefore, we find ourselves in a vicious circle, characteristic of the traditional approach to risk extrapolation (see fig. 1). A mathematical model supposedly intended to furnish the extrapolation procedure with some additional information actually yields dose risk values so low that they have roots only in epidemiological data. Consequently, the linear-quadratic equation appears to be a tool to stretch the low-dose tail of the empirical data into the range of lower dose values, disregarding the role of any *a priori* information.

To ensure persuasive extrapolation, this information should correspond to "the nature of phenomena" in radiation oncogenesis and should also be expressed in adequate mathematical terms. This idea is easier said than done.

For example, is there any reason to search for a model which would ensure better fitting epidemiological data than any other model? The question may be formulated better as follows: does a better statistical fitting of epidemiological data indicate that the model used is in better correspondence to the "nature of matters" and, respectively, ensures more persuasive extrapolation? Contrary to popular opinion, we have to give an unambiguously negative answer. This approach may lead to obtaining incorrect results by means of good statistical treatment of the data. A number of examples of such situations with the treatment of dose-stochastic effect curves are addressed in our previous publications [2,3].

2. THEORETICAL APPROACH TO THE RISK EXTRAPOLATION

We have called our approach "theoretical" due to the direct inclusion of theoretical considerations into the extrapolation procedure. The general idea is to improve the informational content of an epidemiological dose-effect curve by referring unequivocally to relevant scientific knowledge belonging to adjacent disciplines. This is the knowledge beyond the field of epidemiology of radiogenic cancer, in areas of theoretical oncology, molecular

oncology, animal data on cancer induction, and radiobiology of target cells for radiogenic cancer induction (see Fig. 2.).

Undoubtedly, knowledge accumulated in molecular oncology, for example, would in some way influence the construction of the "truthful" dose-response model. However, until we transform this knowledge into a certain theory of radiogenic cancer induction, it remains impossible to identify both the particular aspects of the model which could be modified, and the proper directions of this modification. This type of theory must result in a "theoretical" mathematical model of dose-effect relation to serve as an effective tool of its persuasive extrapolation to low dose region.

Such a specific "prognosis-oriented" theory has only one feature commonly associated with the world "theory"; it operates with some entities that were never directly observed. In any other respect, this theory could disappoint a "pure theorist", since its other features make it quite different from other theories.

First, extrapolation of the risk must be perceived as persuasive, which is why such a theory must result strictly from well established current knowledge, and involve the knowledge in the risk extrapolation procedure without adding new hypotheses.

Second, such a theory must be multidisciplinary. It should be operable in every area of knowledge considered influential in a conceptualized dose-response relationship. Meanwhile, it should not concentrate on any specific aspect of carcinogenesis.

Third, instead of focusing on "the complicity of phenomena", such a theorist should defer identification of the specific knowledge relevant to the risk extrapolation and make it unequivocally interpretable in mathematical terms, thus facilitating the construction of a theoretical model of dose-effect relationship for radiation-induced cancer intended for risk extrapolation.

Thus, in the frame of concept, the following are contributors to the extrapolation procedure (see Fig. 2):

- fundamental mechanistic knowledge predetermining the general mathematical construction of dose-response model;
- certain specific data belonging to this knowledge and resulting in values of theoretical parameters of the model;
- epidemiological data influencing values of the free model

parameters estimated by model fitting to observed dose-response graph.

3. CONSTRUCTION OF THE MATHEMATICAL MODELFOR DOSE-RESPONSE RELATIONSHIP.

We have condensed necessary elements of the existing mechanistic knowledge which are fairly well accepted and/or are derived from the available data into the following set of statements:

1. A malignant neoplasm is a clone grown from a single cell initiated by radiation exposure.

2. Clones of potential tumor progenitor cells grow independently of each other in the host organism, until one of them transits to the phase of irreversible tumor progression.

3. Radiogenic cellular events-initiators of induced tumor growth involve so-called "two-track" effects in target cells.

4. All important features of initiated cells, including their radiosensitivity, are indistinguishable from those peculiar to their normal homologues at an early stage of cancer growth.

5. Any radiation-induced precarcinogenic event in a target cell can initiate growth of only one specific type of malignant neoplasm.

Every postulate together with its corollaries matches its mathematical component in the following general equation for dose-effect relationship I(D) for single exposure at the dose D:

$$I(D)=1- \exp<-\alpha_o \bullet f(D) \bullet \{1- \exp[-\beta_o \bullet \exp(f(D))]\} \bullet \exp[-f(D)]> \qquad (2)$$

For example, a particular corollary of statements 3 and 4 is: dose-response relationship $f_i(D)$ for initiating effects in target cells is

similar to $f_1(D)$ for lethal ones since both belong to the same group of two-track effects inducted in the same cells within the similar mechanism. The only essential difference between $f_i(D)$ and $f_1(D)$ is some a constant multiplier ψ:

$$f(D) = \psi \bullet f_i(D) = f_1(D) \qquad (3)$$

Equation (2) operates with a specially created [3] "theoretical" model of f(D) as a version of the theory of dual radiation action [4]. We have improved it by ensuring a more adequate realization of its general postulates. This provides us with the procedure to assess the slope of the curve f(D) resulting from very low level exposure. The parameters of f(D) are derived mostly from target cell radiobiology and are particular for biological species, target tissue, and radiation quality. One of them is the mitotic index of target tissue. In the model, it influences the assigned initial slope of f(D). All these parameters of f(D) are theoretical in terms of our model I(D) of describing dose dependence for radiation-induced cancer.

The model I(D) also includes two free parameters: α_o and β_o. We derive their values through maximum likelihood estimation fitting the model (along with all its theoretical patterns) to empiric dose-response relation(s). The first parameter, α_o, is of the normalizing sort, while the second, β_o, has a clear biological meanin; it is the probability of tumor growth per one initiated cell.

Instead of discussing the structure of the general equation (2), I would like to clarify two possible extreme situations connected with the value of β_o when it is lower than 0.01 or high enough (up to 1). The latter should mean that any initiation event in a target cell would result in tumor growth.

Postulate 4 deals with the identity of characters of initiated cells and their "normal" homologues. This influences the theoretical dose-effect relationship by taking into account the effect of postirradiation compensating hyperplasia of stem cell pools.

For example, consider that irradiation of 10 stem cells has produced initiating events in two of them (see Fig. 3). Let this be a median lethal dose, so that out of any two initiated cells, only one remains able to give the tumor growth. After a complete

repopulation, however, the overall number of clonogenic cells will reach its basic value (i.e., 10) with two initiated cells again among them.

Repopulation has to also restore the "preinactivation" number of initiated cells because each of them, in general, fully participates in the repopulation process. This results from their functional identity as normal cells at an early stage of tumor induction.

The question which has, thus far, escaped the attention of specialists dealing with dose-response models for radiation-induced cancer is: if postirradiation hyperplasia restores the basic number of initiated cells, does it mean that inactivation should not affect dose-response relation at all? Our answer is: not altogether. It depends on the value of the probability β_o of tumor growth per single initiated cell.

There may be two extreme situations here. First, let this probability be low. After the repopulation process is completed, each descendant of any initiated cell can give its contribution to overall probability of tumor growth if it remains low. Within this situation, repopulation effects completely compensate those of inactivation, hence, the dose-response curve for radiation-induced cancer will look like that for initiation events in target cells (see Fig. 4).

Alternatively, let this probability be rather high. Let it be equal to 1 for simplicity's sake i.e., every initiated cell gives rise to tumor growth. All repopulation descendants of a primary initiated cell, after repopulation is completed, bear precarcinogenic change in their genome identical with that in their progenitor. Therefore, only one tumor can accrue from all these cells either with or without repopulation. Thus, in this situation, inactivation is not compensated by repopulation, and the dose-response curve will reflect well known initiation/inactivation competition (see Fig. 4 again).

All this, stated above in biological terms is fully realized in the mathematical structure of our general dose-effect equation (2). These two situations are described in the following extremely simple forms:

If β_o is about 0, then:

$$I(D) = \alpha_o \bullet \beta_o \bullet F(D) \qquad (4)$$

If β_o is about 1, and D is high enough then:

$$I(D) \approx \alpha_o \bullet \beta_o \bullet F(D) \exp(- f(D)) \qquad (5)$$

Obviously, Eq. (4) realizes the form of the model curve regularly growing with the dose. It is identical to the usual "linear-quadratic equation without inactivation term." This behavior of dose-response relationship reproducing the same relationship for the induction of two-track initiation effects (chromosome exchanges and interstitial deletions) is peculiar to leukemia induction in humans.

Another situation results in the model curve (5) reaching its maximum at some definite dose value, that is, a marked "optimal leukemogenic dose" is observed. This is peculiar to leukemia induction in mice by singe irradiation. Thus, two distinct variants of dose response relationships were explained at least qualitatively, in the framework of the single mechanism of tumor induction. The quantitative explanation of observed dose-response relationships is also possible, due to the descriptive capabilities of our theoretical equation.

4. MODEL FITTING TO DOSE-RESPONSE RELATIONSHIPS AND RISK EXTRAPOLATION

Using direct calculations, we have ascertained that, by adjusting only two free model parameters, it is possible to obtain a sucessful application of any dose-response curve for radiogenic cancer induced by a single irradiation of humans or laboratory animals. The only exception is thymic lymphoma in mice, which is known to be induced by indirect mechanism [5]. However, we consider the descriptive capabilities of a theoretical model confirmatory evidence that operating with dose-response relationships using this model is valid for reasons beyond the mere value of its basic postulates and the adequacy of its mathematical construction.

Moreover, a successful application of the model to any isolated dose-response relationship is not a reliable method of testing its descriptive capabilities. Its application to the data on radiation leukogenesis would be a better test because, in this the case, pairs of dose-effect relationships are available which were obtained with the same animal species, but for different levels of radiation.

Fig. 5 and 6 present the results of applying such pairs of dose dependencies, as well as 75%-confidence limits for values of free parameters derived through likelihood estimation. This data shows that, within a unified model applied to a pair of the empiric dose-response relationships (for neutrons and gamma-rays), the confidence limit appears smaller than that resulting from the separate application. Also, a "unified" confidence area belongs to intersection of the "separate" areas corresponding to independent parameter adjustment.

This raises the hope that our general equation (2) actually has an important feature of a theoretical approach implementation. This model seems able to unify separate groups of data which resulted from separate observations but actually belong to a single general integrity or universe.

We have estimated free model parameters corresponding to epidemiological data on A-bomb survivors [6, 7] by likelihood estimations within unified fitting of Eq (2) to data of both cities for each cancer site where clear dose-response curves had previously been obtained. Then we evaluated the initial slope of the model curve describing the Nagasaki data as the risk per unit dose, provided it is delivered at a very low dose rate (see Fig. 7). Its inverse relation to the risk coefficient derived from the linear extrapolation of the same data was interpreted DDREF. The resulting DDREFs are listed in Table 1 with derived values of mitotic index of each target tissue.

Listed below are two groups of estimated DDREFs. These are the expected "most probable" values and "parametrically minimal" ones. The "parametrically minimal" values, which are the conservative values of DDREFs resulting in the upper bound of low-level risk evaluation, appeared to be rather similar for all (about five) cancer sites listed.

We intentionally represent our results on the risk extrapolation in a form of DDREFs instead of low level risk coefficients. Obviously, DDREFs are of lower susceptibility to any further variations of epidemiological data, for instance, due to application of the DS-86 dosimetry system.

DISCUSSION

It should be noted that, contrary to current approaches, epidemiological data slightly modifies DDREFs estimated here. As is shown by equation 2, they are mostly based on the relevant knowledge derived from the adjacent disciplines.

Our theoretical construction could be considered incomplete, particularly since it deals only with the process of cancer initiation and does not take into account the "multistep" character of cancer induction, i.e., the "promotion" stage is ignored. However, this is untrue.

First, we take into consideration the "fast autopromotion action" of a single irradiation resulting from hyperplasia of stem cell pools. Second, our equation (2) is a simplified form of the more general equation [3] operating the dose-specific value of the probability $\beta_o(D)$ of tumor growth per each initiated cell.

Such a detailed version could be useful for implementing a more complicated construction of theoretical dose-response relationship. For instance, it would be of interest to treat animal data obtained with protracted exposure to low-LET radiation (from incorporated strontium, for example) along with data obtained with the same animal species but for high-LET irradiation, (from radium, for instance). Theoretical treatment of such a pair of experimental curves could provide better comprehension of low level/low LET risk problems, including the possible role of tissue renewal in radiation carcinogenesis. However, it should be noted that our version of the theoretical model is a "prognostically-oriented" one and has been intentionally simplified for DDREFs estimated to be persuasive. Hence, it deals with two extreme methods of dose delivery: single exposure at a very high dose rate, on one hand, versus an exposure to very low level radiation. One can see that disregarding further possible "autopromotion" effects of a single exposure under our approximation (i.e. β_o is dose-

independent) can lead to overestimated values of extrapolated risk. Also, overestimation of possible low level risk holds valid for any other intentional simplifications of "the nature of matters" involved into our evaluation of DDREFs.

Evaluated DDREFs have their roots in the knowledge adjacent to the procedure of risk extrapolation. Instead of simply stretching the observed dose-response relationships from high doses to lower ones, therefore, our main result is, to a lesser degree, associated with the estimated unique DDREF value, rather than its essence. Figure 5 is the low boundary of DDREF value resulting from theoretical approach to derivation of low level low LET radiation risk. Thus, one can consider it as the "theoretical contribution" to the problem of DDREFs substantiation.

Another result revealed is a possibility to construct a "theoretical" dose-response model deduced solely from fundamental knowledge. It is worth emphasizing that the set of postulates underlying our theoretical model plays the role of a "first-hand tool" to make use of knowledge accumulated beyond the sphere of epidemiology of radiogenic cancer. These postulates could not be proved within this area of knowledge and each of them is a kind of "axiom" here. It should be noted, however, that the "set of axioms" constructed appears to be biologically sufficient to serve as the base of the theoretical estimation of low level risk, which is more reliable, the more "truthful" they are. Hence, there is another advantage of "axiomatic constructions" in addressing the problem of low level risk assessment.

Let us consider this set of axioms transformed from the affirmative into interrogative form. This can provide an exhaustive list of further questions addressed to the current knowledge, not only to examine the reliability of assessed DDREFs, but also to improve such assessment, at least for very low levels of radiation. This can be clarified starting with the last transformed postulate:

1. Can any radiation-induced precarcinogenic event in a target cell really initiate growth of only one specific type of malignant neoplasm? To date, molecular oncology has accumulated much compelling evidence within the area of oncogene activation research.

2. Are important characteristics of initiated cells really indistinguishable from those peculiar to their normal homology at

an early state of thier growth? This complies with the well established concept of tumor progression.

3. Is a malignant neoplasm really a clone grown from a single target cell? Monoclonal origin of malignant neoplasms has become an irrefutable opinion in theoretical oncology.

4. Do radiogenic cellular events, initiators of induced tumor growth, really involve two-track effects in target cells? This statement was first presented at the beginning of the 1980's [8,9].

At that time, we based this statement mostly on the comparative analysis of dose rate dependencies of cancer induction in animals along with those peculiar to induction of endpoints observed in target cells. We had classified the latter into two broad categories termed "one-track" and "two-track" effects. We assumed that non-lethal effects assigned to the last group (i.e., symmetrical chromosome exchanges and interstitial deletions) were to play the role of initiation events in radiation carcinogenesis [8,9]. Moreover, the lethal cell effects also belong to this group of the endpoints. In turn, it allows the creation of a bridge between well observed cell inactivation and cancer initiation, within our concept.

It is known that this supposition was eventually expanded with the oncogene concept. Overexpression and/or abnormal expression of oncogenes resulting in (radiogenic) tumor growth is due to chromosome rearrangements drawing an oncogene together with its gene promoter and/or separating it from its suppressor. Therefore, the two-track effects actually become radiogenic tumor inductors. Good experiment- based confirming evidence can be found in [5, 10].

One question remains: to what extent can radiation- induced point mutations in oncogenes and/or in gene-regulators participate in the process of radiogenic tumor induction? This remaining question is obviously more simple and concrete than the ordinary one which arises in any discussion of the mechanism of radiation carcinogenesis: "What is the nature of the primary event leading to cancer growth"? The possibility to make remaining questions even more concrete, rather than creating problems which will take several decades to be clarified, is a significant advantage of axiomatic constructions.

Such a construction can also provide us a more readily available way of obtaining the answer. For example, it can be shown that this last question could be replaced by the following one: "What is the maximum possible value of RBE for cancer induction by high-LET radiation?" This, in turn, could result from a special RBE-oriented animal study. The well known work [11] is a good example of such a study.

Finally, Figure 8 unites all known data obtained on radiation leukogenesis in humans, especially that resulting from irradiation at "decreased" dose rates as compared to those observed in A-bomb survivors. Every group of available data resulting in estimated risk is enclosed within a rectangle, reflecting its uncertainty both in dose rate and the assessed risk. One of the results of comparing this data together can be formulated as follows: the more effective the theoretical contribution of the DDREF projection is, the easier the epidemiological data can be interpreted.

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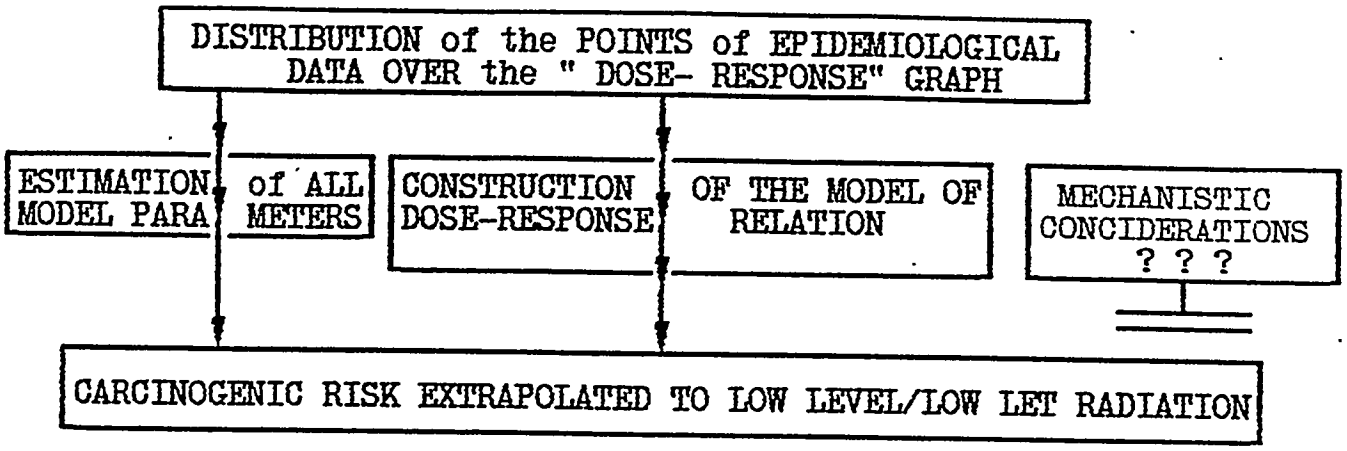


Fig 1.

Ordinary approach to the risk extrapolation.

No additional information is involved into the risk extrapolation procedure. Extrapolated values of the risk have their roots only in epidemiological data themselves.

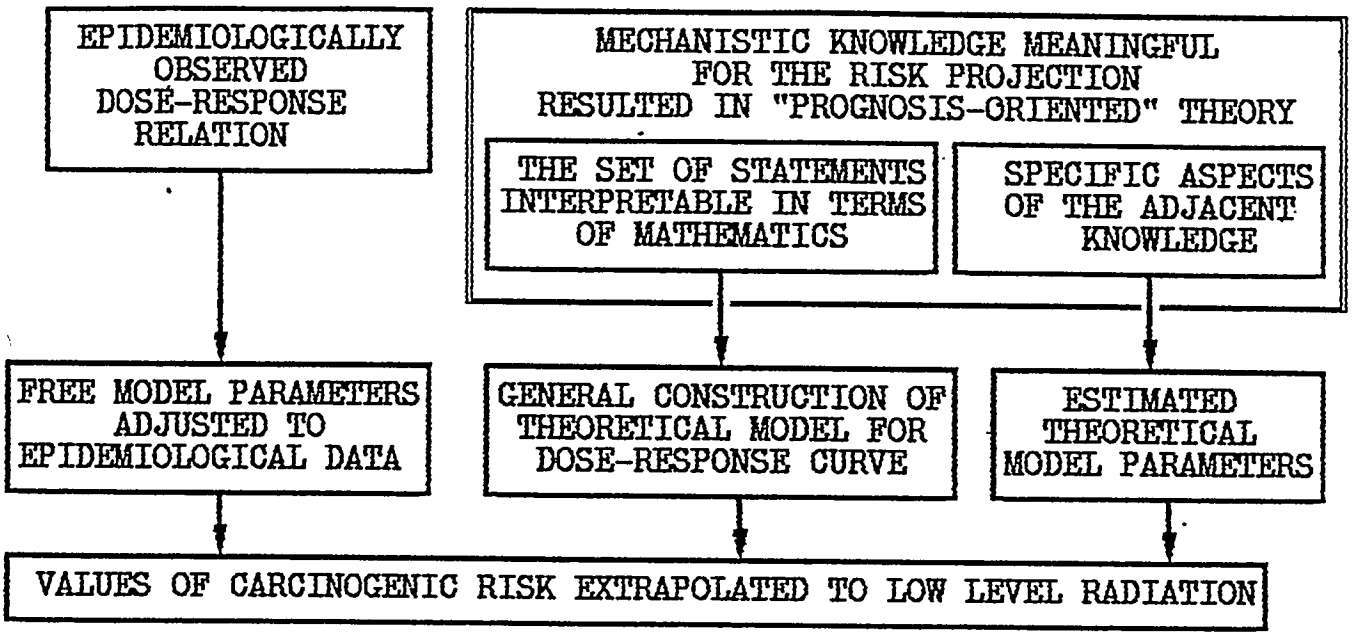


Fig 2.

Theoretical approach to the risk extrapolation.

The adjacent knowledge is involved inequivocally into this procedure through general construction of a mathematical model for dose-response relationship and its theoretical parameters estimated on the base of specific data. Epidemiological dose-response relationship has its influence on the free model parameters.

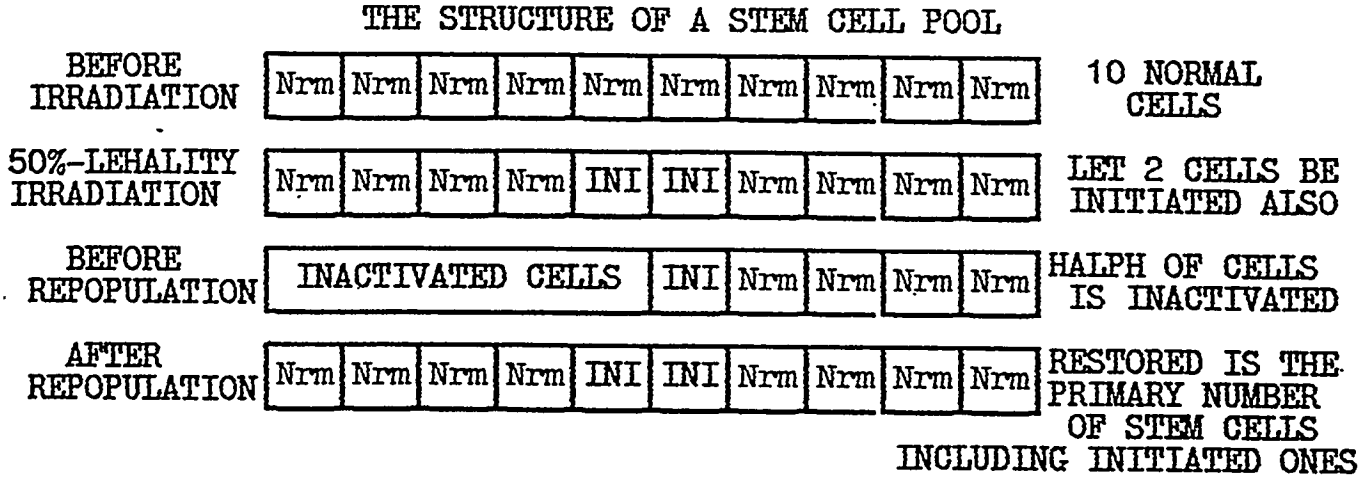


Fig 3.
Schematized presentation of the process of an irradiated stem cell pool restoration.
Cell death-induced hyperplasia restores the initial number of normal cells as well as initiated ones and so that forms the behavior of dose-response relation for induced cancer.

Normal and initiated cells are designated as Nrm and INI respectively.

HAS INACTIVATION OF INITIATED CELLS NOT AN INFLUENCE ON DOSE-RESPONSE CURVE AT ALL?

IT DEPENDS ON THE PROBABILITY OF TUMOR GROWTH β_0 PER ONE INITIATED CELL

Nrm	Nrm	Nrm	Nrm	INI	INI	Nrm	Nrm	Nrm	Nrm

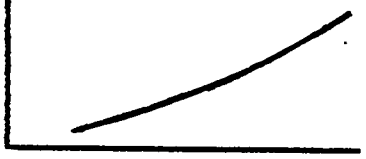
THERE ARE TWO EXTREME SITUATIONS HERE:

PROBABILITY β_0 IS QUITE LOW:	PROBABILITY β_0 IS UP TO 1:
REPOPULATION PROCESS COMPLETELY COMPENSATES INACTIVATION ONE	INACTIVATION IS NOT COMPENSATED BY REPOPULATION PROCESS

THESE TWO SITUATIONS ARE REALIZED IN TWO SIMPLE FORMS OF THE EQUATION:

$$I(D) = \alpha_0 * \beta_0 * f(D)$$

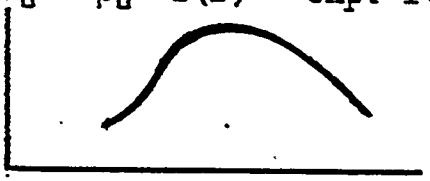
LEUKAEMIA INDUCTON IN HUMANS



NO ROLE OF INACTIVATION IN DOSE-RESPONSE CURVE

$$I(D) \approx \alpha_0 * \beta_0 * f(D) * \exp[-f(D)]$$

LEUKAEMIA INDUCTION IN MICE

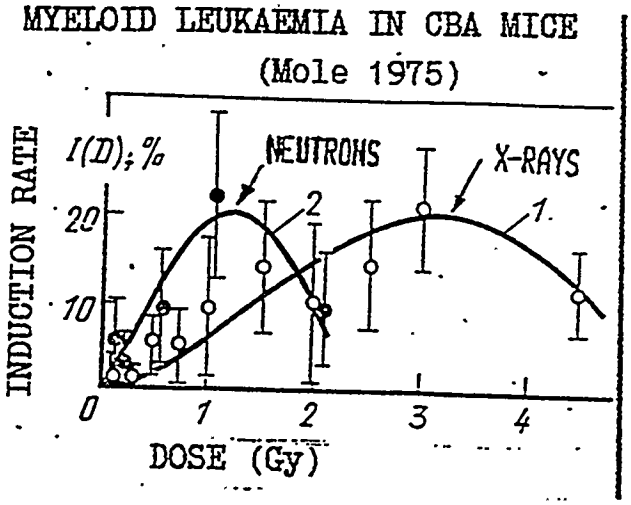


A MARKABLE ROLE OF INACTIVATION IN DOSE-RESPONSE CURVE

Fig 4.

Theoretical model appears able to explain the existence of the two extremely distinguishing variants of the behavior of dose-response relationship for leukaemia induction in animals and humans within the unique mechanism.

Both types of behavior have their roots in inactivation of initiated cells but "species-specific" result of its influence on dose-response relation depends firmly on the probability of tumor growth per one initiated cell.



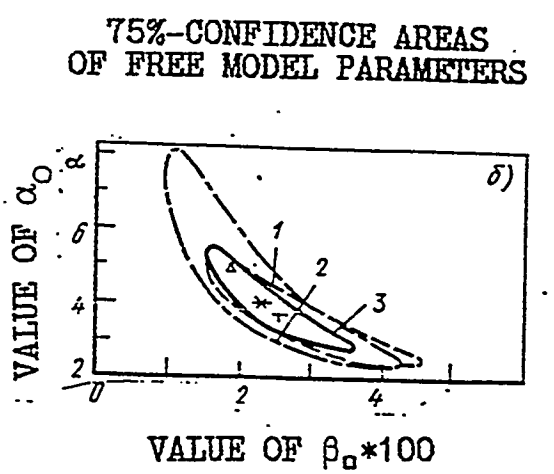


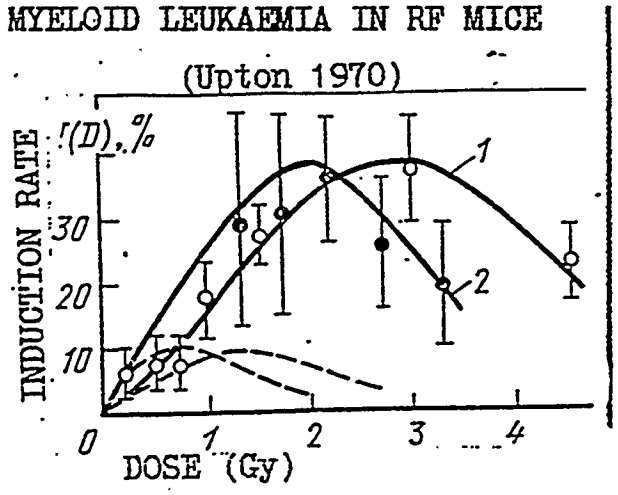
Fig 5.

The model fitting to a pair of dose-response relationships obtained by Mole (1975) with the same animals species but for different kinds of radiation.

—— - Enclosed is the area corresponding to "unified" model fitting to pair of observed dose dependencies.

- - - Area corresponding to model fitting to one of separate dependencies.

Values of the model parameters for the best fitting to pair of dependencies are: α_0=3.8; β_0=0.028;



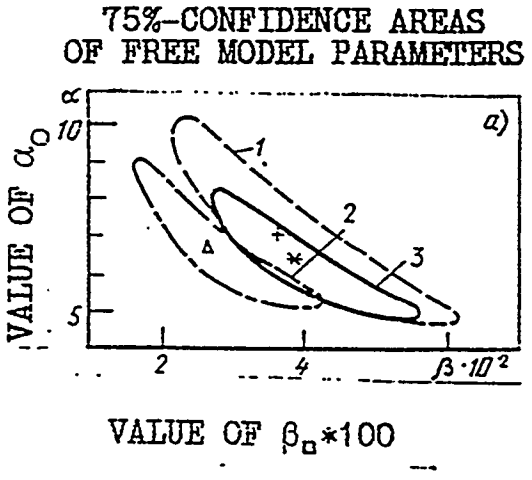


Fig. 6.

The model fitting to a pair of dose-response relationships obtained by Upton (1970) with the same animals species but for different kinds of radiation.

—— - Enclosed is the area corresponding to "unified" model fitting to pair of observed dose dependencies.
- - - Area corresponding to model fitting to one of separate dependencies.
Values of the model parameters for the best fitting to pair of dependencies are: $\alpha_0=6.5$; $\beta_0=0.04$;

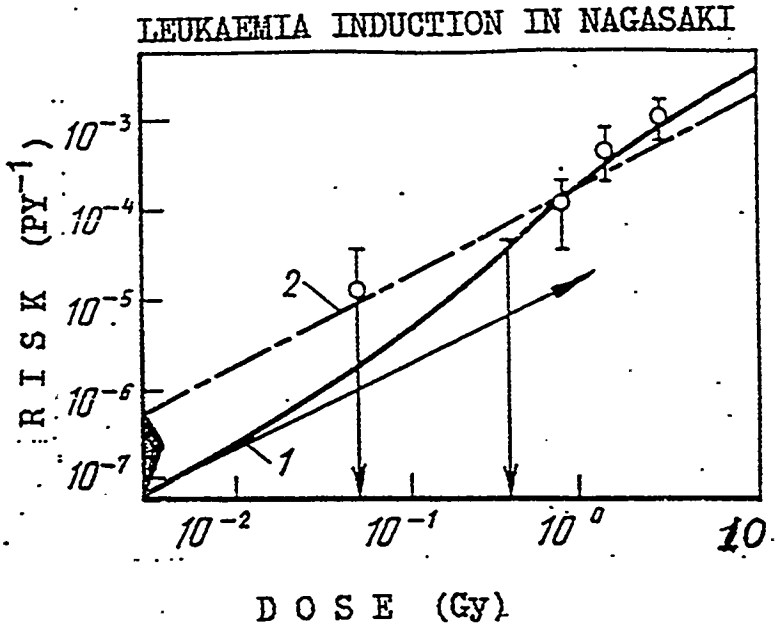


Fig 7.

An example of the extrapolation of epidemiologically measured risk to low level/low LET radiation for leukaemia induction (Ishimaru at al 1979).

——— - model curve fitted to Nagasaki data;
———→ - risk projection for low level/low LET radiation;
- - - - linear extrapolation of the risk;
▶ the length of this section of the ordinate axis is estimated value of DRCF for leukaemia induction.

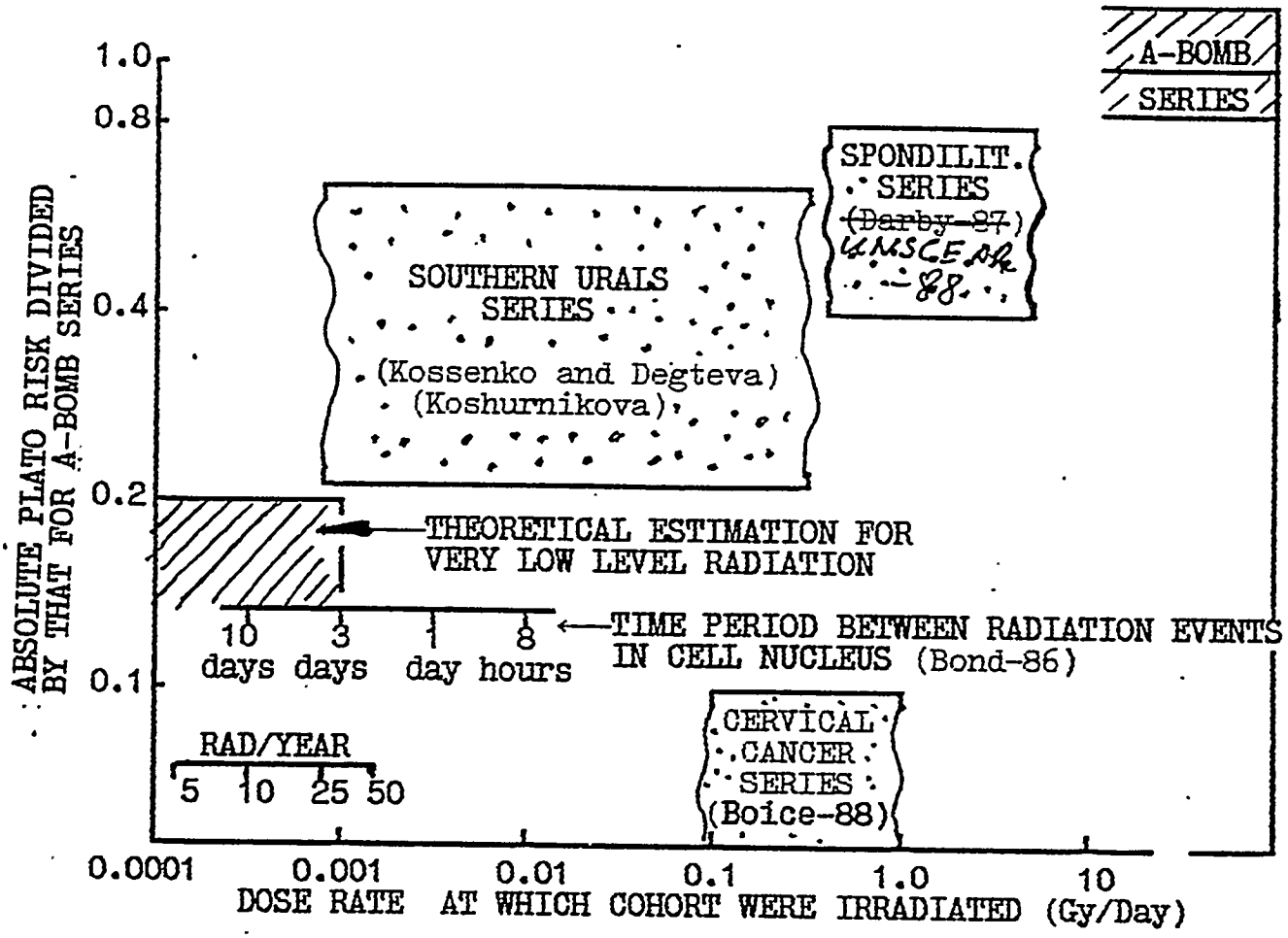


Fig 8.

Current situation with leukaemogenic risk assessment in cohorts exposured at decreased dose rate (approximately). The assumed position of every group of data is enclosed by the area of its vagueness corresponding to the scale of this graph.

Table 1. Dose rate correction factors DRCFs resulting from the theoretical approach to extrapolation of the risk values to low level/low LET radiation.

Cancer site	Upper estimation of mitotic index of target tissue tissue	Asigned value of DRCF	
		Anticipating value	Low bound estimation
Leukaemia	2 %	7	5
Mammary cancer	1 %	12	7
Lung cancer	0.5 %	8	6
Thyroid cancer	0.1 %	14	5

Some Results of Long-Term Investigation Population Exposed as a Result of Release of Radioactive Wastes into the Techa River in Southern Urals

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Part 1. Exposure Situation and Dose Reconstruction Method.

1. Exposure Situation on the Banks of the Techa River.

During the period 1949-1956, faults in the technology of the Mayak plutonium production facility allowed wastes from the radiochemical plant to be discharged into the Techa River. During that period, 76 million m^3 liquid wastes with 2.75 million Ci of beta radioactivity were dumped into the river [1,2]. About 95% of the total radioactivity was released between March, 1950, and November, 1951. The average daily release in that period was 4,300 Ci, with the following radionuclide composition: 8.8% of ^{89}Sr, 11.6% of ^{90}Sr, 12.2% of ^{137}Cs, 26.8% of isotopes of rare earth elements, 23.6% of ^{95}Zr-Nb, 25.9% of $^{103,106}Ru$. During the next five years, radioactive releases into the river system decreased considerably, totaling 9.5 thousand Ci per year in 1952, and ranging from-0.5 to 2 thousand Ci annually in the period 1953-1956 (Fig. 1).

In 1956, the river bed of the Techa was dammed and the migration of radioactive substances to the lower reaches of the river decreased to approximately 0.5 Ci per day. The construction of another dam in 1963 practically isolated the contaminated upper Techa. The above mentioned releases resulted in radioactive contamination of the river system consisting of the interconnected rivers Techa, Iset and Tobol. The most hazardous situation developed on the banks of the Techa. The concentration of radionuclides in the water of the river Iset, downstream of the mouth of the Techa, decreased about 10 times (mostly as a result of dilution), and in the river Tobol, downstream of the mouth of the Iset, the concentration was 100-1000 times lower.

Systematic measurements of radionuclide concentration in the river waters, sediments and floodplain soils, and measurements of

exposure gamma dose rates as well as studies of the radionuclide composition in the contaminated areas began in the summer of 1951. The results of the total beta radioactivity measurements in the Techa River downstream of the release site in that period are shown in Figure 2. Concentrations of radionuclides in the river water decreased sharply in 1952, in comparison with the previous year. Later, however, the decline of concentration slowed down. This may be explained by the fact that about 70% of activity released in 1950-1951 was transferred to sediments of the Koksharov and Metlinsky ponds situated upstream from the Techa and about 10% was transferred to sediments of the lower reaches of the river, within approximately 80 km of the release site. During the subsequent years, the contaminated sediments became a source of secondary contamination of the river water.

Figure 3 shows the results of measurements of gamma radiation along the edge of the Techa. The main source of gamma radiation was radioactive silt, which was practically not shielded by the water layer near the bank strip (Fig. 4). After a sharp decline in releases at the end of 1951, the dose rate of gamma irradiation in the bank strip did not actually change with time. This may be because the main contribution to the contamination of sediments was made by long-lived cesium-137.

Thus, the radioactive contamination of the Techa-Iset river system was caused mostly by massive releases in 1950-1951, when about one fourth of the total activity fell on long-lived radionuclides cesium-137 and strontium-90.

As a result of the contamination of the river-system, 124,000 residents of the Techa riverside communities were exposed to radiation in the Chelyabinsk and Kurgan regions, and 28,100 received significant doses in terms of potential health effects.

The situation on the Techa was aggravated since the river was the main and, sometimes, only source of household and drinking water supply for the inhabitants of the villages along its banks. Wells were scarce; they were used only by a portion of the inhabitants and not for all needs, because the water tasted badly. The river water was used for watering cattle, breeding waterfowl, irrigation, fishing, bathing, washing etc.

In April and May, 1951, an extraordinarily powerful flood led to radioactive contamination of the surrounding lands. The floodland had been used by some inhabitants for cattle-breeding and haymaking. Previously, radionuclides had been injested by the inhabitants mainly with water; after the flood the contribution made by agricultural products began to increase with consumption of milk and vegetables from flooded kitchen gardens.

In 1953, the use of river water for household needs, drinking, fishing, breeding waterfowl and bathing was banned. The most heavily contaminated part of the floodlands was excluded from land tenure. Simultaneously, the construction of wells began, but it continued slowly, due to interruptions. By the end of 1954, all residents on the Techa and their cattle were supplied with water from ground springs. But for some reason, consumption of water and its use for other household needs continued until 1956, although it was reduced to some extent when a special "river militia" was set up to ensure control in all communities along the bank of the river.

In the first years after the beginning of the exposure, there were 39 villages on the banks of the Techa River. In 1953, the evacuation of the village of Metlino was started. Metlino had the most unfavorable conditions because it was located within only 7km from the site of release, on the banks of the settling pond. The entire popuation of the village (1,200 people) was evacuated by 1956. In the period 1956-1960, the inhabitants of 19 other villages (6,300 people) were moved to locations far from the contaminated river.

Thus, the analysis of exposure conditions shows that the main portion of the dose was received by the people in 1950-1956, due to the close proximity of the river. The exposure situation during that period was highly dynamic; there were changes in activity and nuclide composition of releases and hydrological regime on the river. Also, protective measures were being taken at that time. These combined factors made the task of dose reconstruction for exposed population extremely difficult.

2. Estimation of External Radiation Doses

The measurements of gamma dose-rate along the riverbank, on the shore, within a few hundred meters of the water, and in specified areas of villages and indoors were used to estimate the absorbed doses of external irradiation. The results of these measurements

were obtained from the technical reports prepared by a special team from Moscow Biophysics Institute, supervised by Professor Alexander Marey. Unfortunately, these reports do not provide enough detail to judge the accuracy of the measurements, but no other data was available on gamma-radiation along the Techa River in the early 1950s. The measurements were started in the upper reaches during the summer of 1951 and, since 1952, have regularly been made along the entire Techa. Radionuclide concenrations were measured annually along the entire river, and two to five times a year in specific reference sites along the upper reaches of the Techa. On the basis of these measurements, we reconstructed the average annual levels of exposure for the most commonly visited sites in each of the riverside villages.

Through monitoring of typical lifestyles for different age groups of riverside residents in the 1960's, Melkhior Saurov, of the Moscow Biophysics Institute, estimated the time people stayed in each of the specified sites with different dose rates. This approach provided an opportunity to assess the average annual absorbed doses from external radiation for each village in total and for every age group in each village (Table 1). Unfortunately, the reports prepared by Prof. Saurov did not show the variations in typical lifestyles, therefore, we were unable to estimate the distribution of individual external doses in villages on the basis of his data. Consequently, the estimations of external doses should be considered tentative. The dependence of average whole-body doses of external radiation on the distance along the Techa from the release site is shown in Fig. 5. Average values were calculated for each village, taking account of age distribution.

The highest dose rates were observed in 1951, although the levels for 1950, reconstructed on the basis of an assumption about a certain contribution of gamma-radiation and average annual beta-activity of releases, were not much lower. Accumulation of external radiation doses actually stopped after 1956, when all residents upwater of the Techa were resettled and, in the other villages, the contaminated floodplanes were fenced off.

The highest cumulative external doses were received by the inhabitants of Metlino, where average values for age groups were estimated as 0.50-1.0 Gy per year in 1951. However, the range of individual doses due to variability of gamma levels on the territory of the village was estimated as 0.05-2.0 Gy per year. In the Kurgen

region, which is in the lower reaches of the river and is more than 150 km from the site of release, doses of external radiation did not exceed 10 Gy per year, even in the period of massive releases.

3. The content of strontium-90 in human organism. Estimation of radionuclide ingestion rates.

To calculate the tissue doses of internal radiation it is necessary to know the dynamics of accumulation of radionuclides in organs and tissues of an individual. The main dose-forming radionuclide released into the Techa and ingested by the residents was strontium-90, which is accumulated and stored in bone for a long time. Since 1960, specialists from Branch 4 of the Biophysics Institute in Chelyabinsk have been measuring the surface beta-activity of teeth. Since 1974, they have tested the inhabitants of the Techa River area in the whole-body counter SICH-9.1 to determine how much strontium-90 and cesium-137 these people have absorbed [3-5]. More than 12,000 exposed people have been measured since 1974, when the whole-body counter was developed. The results of numerous measurements showed that there was a clear age dependence of strontium-90 in the whole body and teeth enamel on age (Fig. 6). The maximum content in the body is observed in the people who, during the period of massive releases, were teenagers (13-15 years old) but maximum content in teeth enamel was detected in people who were born in 1950 and ingested the maximum amount of strontium-90 during the first year of life.

The method of reconstruction of ^{90}Sr intake on the basis of beta-count of teeth was developed by V. P. Kozheurov in 1978. The basic concept of this method is as follows: if Y is the content of ^{90}Sr in the teeth of age-cohort born in year T (measured value); X(t) is the content of ^{90} Sr in the diet of adults in year t (unknown); $\alpha(t-T, t)$ is the relationship between ^{90}Sr content in the diet of adults and the diet of children at the age of t-T in the year t (deduced from the relationship of children's to adults' water and milk consumption); a set of equations can be constructed for age-cohorts in which beta-radiation in tooth enamel is detectable (Fig. 6) can be constructed:

$$Y_T = k' \sum_{t=t_{beg}}^{t_{end}} x(t)\alpha(t-T,t)K(t-T)e^{-\lambda_R (t_{mea}-t)}$$

Here: k' is the normalization coefficient; t_{beg} is the year of beginning of ^{90}Sr intake; t_{end} is the year of end of ^{90}Sr intake; t_{mea} is year of measurement of beta-count of teeth; K(t-T) is transfer coefficient "diet-teeth" for age "t-T" (unknown); λ_R is a constant of radioactive decay of ^{90}Sr. We solved this set of equations by "fast descent" method and thus the annual levels of ^{90}Sr were estimated in the diets of adults and children.

Fig. 7 shows reconstructed levels of ingestion of ^{90}Sr for different age cohorts of the reference community, Muslyumovo. Since the radionuclides were ingested mostly with water, the levels of ingestion of other nuclides were estimated on the basis of data on isotope composition of the contaminants of the river water and ^{90}Sr intakes. It was established that, in addition to ^{90}Sr, other radionuclides (^{89}Sr and ^{137}Cs) may be involved. Their levels of ingestion in that period exceeded the limits of annual ingestion according to approved Russian norms of radiation protection. Fig. 8 shows annual ingestion levels of the main dose-forming radionuclides for the adults of Muslyumovo.

4. Age-dependent model of Strontium metabolism in a human body

The model described in our book [6] is applicable for any rate of ingestion of Strontium in human. While elaborating the model, in addition to our data on the long-term retention of ^{90}Sr in skeleton on the Techa, we used the information obtained by other researchers on the content of ^{90}Sr from global fallouts in bones of people inhabiting other regions, as well as experimental results of instantaneous injection of ^{85}Sr into human organisms. For a 40-year old adult, the elaborated model corresponds to Marshal's model from Publication 20 of the International Commission on Radiation Protection [7]. This method enabled us to offset to some extent the lack of reliable information on the initial period of the Techa River exposure situation.

According to the model, the fraction of Strontium left in the skeleton after instantaneous injection at the age of t is changing with time t in the following way:

$$R(\tau,t)=f(\tau)P(\tau)\left[1+\frac{\tau}{\varepsilon(\tau)}\right]^{-b(\tau)}\chi$$

$$\chi\left\{\beta(\tau)e^{-(\lambda_C+\lambda_R)t}+(1-\beta(\tau))e^{-(\lambda_T+\lambda_R)t}\right\}R_{Ca}(\tau,t)$$

Parameter R (τ, t) are functions of age at the initial moment τ:

$f(\tau)$: absorption from gastro-intestinal tract;
$P(\tau)$: initial retention in skeleton;
$\beta(\tau)$: fraction of isotope initially deposited in cortical bone;
$\varepsilon(\tau)$: extrapolation parameter defining the rate of excretion at the initial moment;
$b(\tau)$: power function slope;
λ_C ,λ_T : rate constants of excretion from cortical and trabecular structures of a skeleton for large periods of time (0.0237 and 0.0949 per year);
λ_R : constant of radioactive decay (0.0238^{-1} year for ^{90}Sr and 5.009 for ^{89}S);
$R_{Ca}(\tau,t)$: function showing the decrease of content of radionuclide due to the fact that the content of Calcium in a skeleton begins to decrease starting from some critical age τ_{CR} begins to decrease:

$$R_{Ca}(\tau,t)=\begin{cases}1, & \tau+t<\tau_{Cr}\\ Ca(\tau+t)/Ca(\tau_{Cr}), & \tau<\tau_{Cr},\quad \tau+t\geq\tau_{Cr}\\ Ca(\tau+t)/Ca(\tau), & \tau\geq\tau_{Cr}\end{cases}$$

Dependence of the content of Calcium in a skeleton received on the basis of data in terms of a Reference Man 18] can be expressed in the following way:

$$Ca(\tau)=\begin{cases}28+69.04\tau-13.07\tau^2+1.2506\tau^3-0.03305\tau^4, & \tau<20\\ 900, & 20\leq\tau\leq30\\ 900-.01(\tau-30)^2, & \tau>30\end{cases}$$

Here $Ca(\tau)$ is the average content of Calcium for men and women in skeleton (in grams); τ is the age of an individual (in years).

Dependence of parameters of the metabolism model on age is shown in Fig. 9. Model parameters assessments were obtained by means of fitting model calculations to the different sets of experimental data (Fig. 6 and 10). The content of strontium in a bone was calculated by integrating multiplication of retention function by ingestion rate of strontium in the organism. It is possible to judge the adequacy of the elaborated model by studying Fig. 6 and 10. These figures show the estimates in comparison with the data on the content of strontium in bones of people in different age groups and different regimes of ingestion. The model reflects the major age characteristics of metabolism of strontium maximum: concentration of radionuclides in bone tissue of one-year old children due to chronic ingestion (Fig. 10) and maximum long-term retention in skeletons of teenagers (Fig. 6). This suggested that absorbed doses in red bone marrow (RBM) and cells of bone surfaces (BS), calculated using the given model, are close enough to reality. Transfer coefficients from strontium content in bone to RBM and BS doses from the papers [9,10] were used for the calculations.

In addition to osteotropes (^{90}Sr and ^{89}Sr) a certain contribution to the dose was made by cesium-137, uniformly distributed in the whole body. For the evaluation of doses of internal radiation due to this radionuclide, a model of metabolism from Publication 30 of the International Committee of Radiation Protection [11] was modified to take into account the dependence of "constant" of biological excretion $\lambda(\tau)$ on age τ:

$$R_{Cs}(\tau,t) = e^{-\lambda(\tau)t}\, e^{-\lambda_R t},$$

$$\lambda(\tau) = 2.53\left(\frac{70}{M(\tau)}\right)^{0.74}.$$

Here t is time from the moment of ingestion (years); $R_{Cs}(\tau,t)$ is the retention function of Cesium; $M(\tau)$ is whole body mass (kg) at the age τ; λ_R is 0.0231 $year^{-1}$ which is a constant of radioactive decay for ^{137} Cs.

5. Evaluation of doses of internal irradiation .

Estimates of internal radiation doses to RBM and cells of BS versus age are summarized in Fig. 11 and 12. They show that the youngest age groups were mostly exposed to radiation at the initial period of the exposure However, maximum peaks are noted in dose curves describng later exposure situations due to the cohorts that were teenagers in 1950-1951. This part of the population has proved to be a critical group in terms of levels of accumulated doses. The highest levels were observed in the first years of exposure, which resulted in 80-90% of the accumulated dose of internal radiation being realized within a 10-year period.

For the assessment of population effects, the change in the doses of internal radiation depending on the distance along the river was taken into account. The statistical analysis of the measurements of ^{90}Sr body content in the residents of all villages showed that the variability of "mean-for-village" values (adjusted for age) was caused mostly by two factors: decrease in radionuclide concentration in the downstream river water (factor of dilution by water of tributaries); and the availability of clean water from springs for every village during the period of major releases (in some villages there were no wells and all inhabitants drank river water, other settlements had a good supply of clean well water).

In addition, a certain role probably was played by national traditions, for example, members of Tartar and Bashkir communities drink much tea. Fig. 13 shows the range of mean dose values of internal radiation to RBM (corresponding average values of whole-body counter measurements, adjusted for age distributions) in different settlements, emphasizing the importance of the above mentioned factors.

6. Distribution of exposed population according to accumulated doses

To obtain the correlation of "dose-effect" and evaluation of risk coefficients, total cumulative doses to organs and tissues from all sources of radiation were calculated (Table 2). The distributions of absorbed dose in the body are uneven: the highest levels were accumulated in BS cells and RBM. The degree of unevenness

increases with distance from the site of release in accordance with increasing role of internal radiation.

Fig. 14 shows a "dose portrait" of the exposed population, i.e., distribution of population according to doses to red bone marrow. More than half of the Techa River population, 74%, received doses of less than 0.5 Gy. Such an asymmetrical curve of dose distribution is characteristic of the majority of exposure situations: only a small proportion of the population receive significant doses, i.e., those who live in close to the source of contamination, while larger population groups are affected only by low levels of radiation. In our case, only 8% of overall population exposed to radiation received doses in excess of 1.0 Gy, whereas about 1% received more than 2.0 Gy to RBM. The preliminary assessment of the upper limit of the dose range is estimated at about 4 Gy, but it should be noted that this value may be underestimated. Further research aimed at correcting individual dose assessment is necessary.

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Legends to Figures

Fig. 1. The average amount of radioactivity release per day into the Tech River from 1949 to 1956 and the isotopic composition of the release (according to the data from the Mayak facility's laboratory, Chelyabinsk-65, project director Dmitry Ilyin).

Fig. 2. Total beta radioactivity of the river water (average annual values per liter of water) in early fifties as a function of the distance from the site of release (according to data by D. Ilyin, 1956).

Fig. 3. The results of exposure dose-rate measurements along the river in the early 1950's. The data presented in this and the next figure (Fig 4) were obtained from the Technical Reports of special teams (led by Alexander Marey of Moscow Biophysics Institute.

Fig. 4. The results of exposure dose-rate measurements (summer 1954 and 1955) as a function of distance from the edge of the water in the villages of Techa Brod (18km downstream from site of release) and Muslyumovo (78 km downstream). In the lower portion of the drawings, the shore topography is shown. A sharp decrease in dose-rate corresponds to the border of the territory flooded in spring 1951.

Fig 5. Average cumulative doses from external radiation as a function of the distance along the Techa River downstream from the site of release. Points correspond to the mean values for settlements, calculated considering the age distributions.

Fig. 6. Average values of whole-body counter measurements (open dots) and beta-count rates of teach (closed dots) for different age cohorts of residents in Muslyumovo. Left curve = our model calculation on the basis of mean ^{90}Sr intake levels shown in the next figure (Fig. 7). Right curve = cubic spline circumscribing age dependence of beta-count of teeth.

Fig. 7. Annual levels of strontium-90 intake for different age cohorts of inhabitants of Muslyumovo village reconstructed on the basis of teeth measurements. In the higher portions of the drawing, the age at the beginning of intake is shown (adults = more than 10 years old).

Fig. 8. Annual intake levels of major dose-forming radionuclides for adult residents of Muslyumovo village in relation to modern Russian limits of intake for the members of the public.

Fig. 9. Parameters of strontium metabolism model as a function of the age of man.

Fig. 10. Strontium metabolism model calculations in comparison with the different sets of data on strontium in man. Different regimes of intake are involved: single injection (a) and chronic ingestion with diet (b and c).

Fig. 11. Age profiles of absorbed dose in red bone marrow (RBM) calculated with the help of elaborated models. Input intake levels correspond with the mean values for Muslyumovo village (Fig. 7 and 8). Initial ages correspond to the first year of intake (1950). Numbers beside curves represent years of dose accumulation from the beginning of intake.

Fig 12. Age profiles of total dose from radionuclides in human body (^{90}Sr plus ^{89}Sr plus ^{137}Cs) in RBM and BS for Muslyumovo village. Values for RBM correspond to the sum of values from Fig. 11.

Fig. 13. Average RBM doses from radionuclides in human body for residents of different villages. The values correspond to mean levels of whole body counter measurements adjusted for age distribution in each village. The scattering mainly reflects the proportion of people who drank well-water or river water in 1950-1951, which varies in different villages. Time period of 25 year was taken in calculation of cumulative doses.

Fig. 14. Approximate distribution of total RBM doses in the Techa River Population. Total absorbed dose in red bone marrow was calculated as the cumulative dose of external radiation plus the cumulative (25-year) dose of internal irradiation from ^{90}Sr, ^{89}Sr and ^{137}Cs. Total doses were calculated fro each age group in each village, then these groups of people (with an account of their total numbers) were gathered into six large groups who obtained less than 0.1 Gy; from 0.1 to 0.2 Gy; from 0.2 to 0.35 Gy; from 0.35 to 0.5 Gy; from 0.5 to 1.0 Gy and more than 1.0 Gy.

Table 1

Levels of External Radiation for Different Age Groups of Inhabitants in a Number of Population Localities on the Bank Strip of the Techa River

Name of the village	Distance from the site of release, km	Absorbed dose, 10^{-2} Gy		
		"Children" born in 1944-1950	"Teenagers" born in 1935-1943	"Adults"born in 1934 and older
Metlino	7	106	213	101
Techa Brod	18	99	197	93
Asanovo	27	71	143	68
Nadirovo	48	32	65	30
Muslyumovo	76	5.8	11	5.4
Brodokalmak	109	2.5	4.5	2.4
Russkaya Techa	138	1.9	3.2	1.9
N.Petropavlovskoye	152	1.8	3.1	1.8

TABLE 2

Average Absorbed Doses in the Organs and Effective Equivalent Doses for Residents of Shoreline Villages Along the Techa River

Name	Number of Residents at the Time of Irradiation	Distance from Site of Release, km	Absorbed Dose, 10^{-2}Gy					Effective Equivalent Dose* x 10^{-2}Sv
			Red Bone Marrow	Bone Tissues	Upper Portion of Large Intestine	Lower Portion of Large Intestine	Other Organs and Tissues	
Metlino	1242	7	164	226	133	146	127	140
Techa Brod	75	18	127	148	117	121	115	119
Asanovo	892	27	127	190	97	110	90	100
Nadirovo	184	48	95	180	53	70	44	56
Muslyumovo	3230	78	61	143	21	37	12	24
Brodokalmak	4102	109	14	31	5.2	8.7	3.2	5.8
Russkaya Techa	1472	138	22	53	7.1	13	3.7	8.2
N. Petropavlovskoye	919	152	28	68	8.7	17	4.7	10
Shutikha	1109	202	8.0	18	3.2	5.2	2.2	5.6
Zatecha	1135	237	17	40	5.7	11	3.2	6.6

Fig 1.

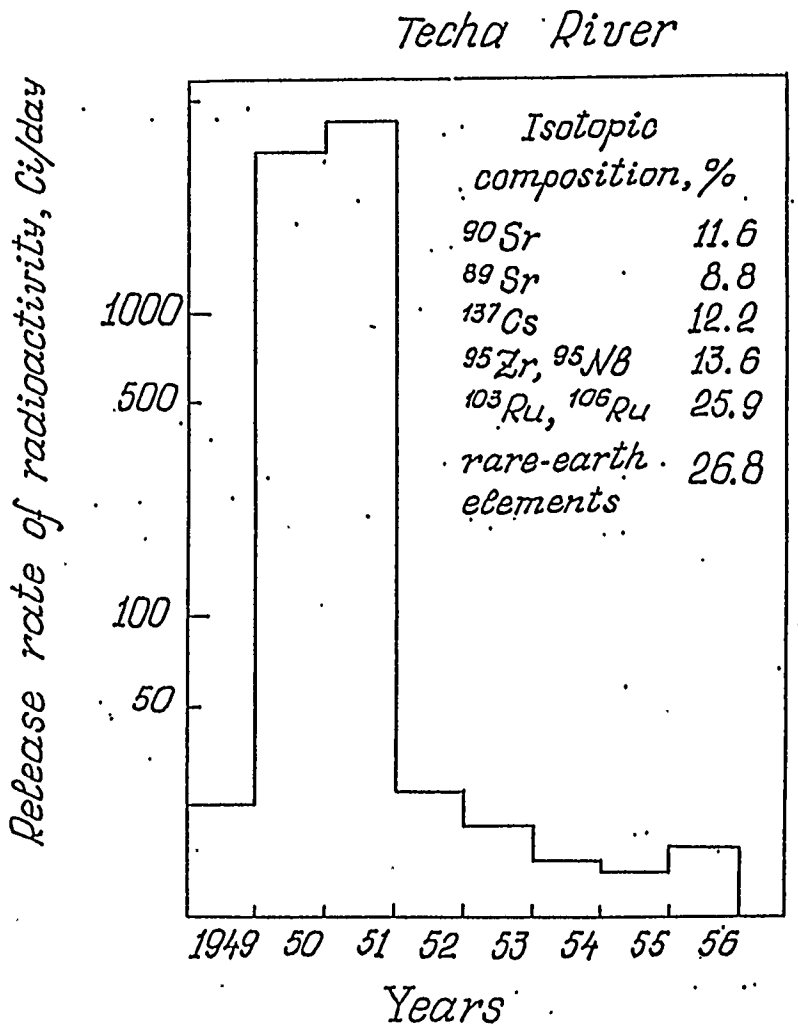

Techa River
Release rate of radioactivity, Ci/day
1000
500
100
50
1949
50
51
52
53
54
55
56
Years
Isotopic composition, %
^{90}Sr 11.6
^{89}Sr 8.8
^{137}Cs 12.2
^{95}Zr, ^{95}Nb 13.6
^{103}Ru, ^{106}Ru 25.9
rare-earth elements 26.8

Fig 2.

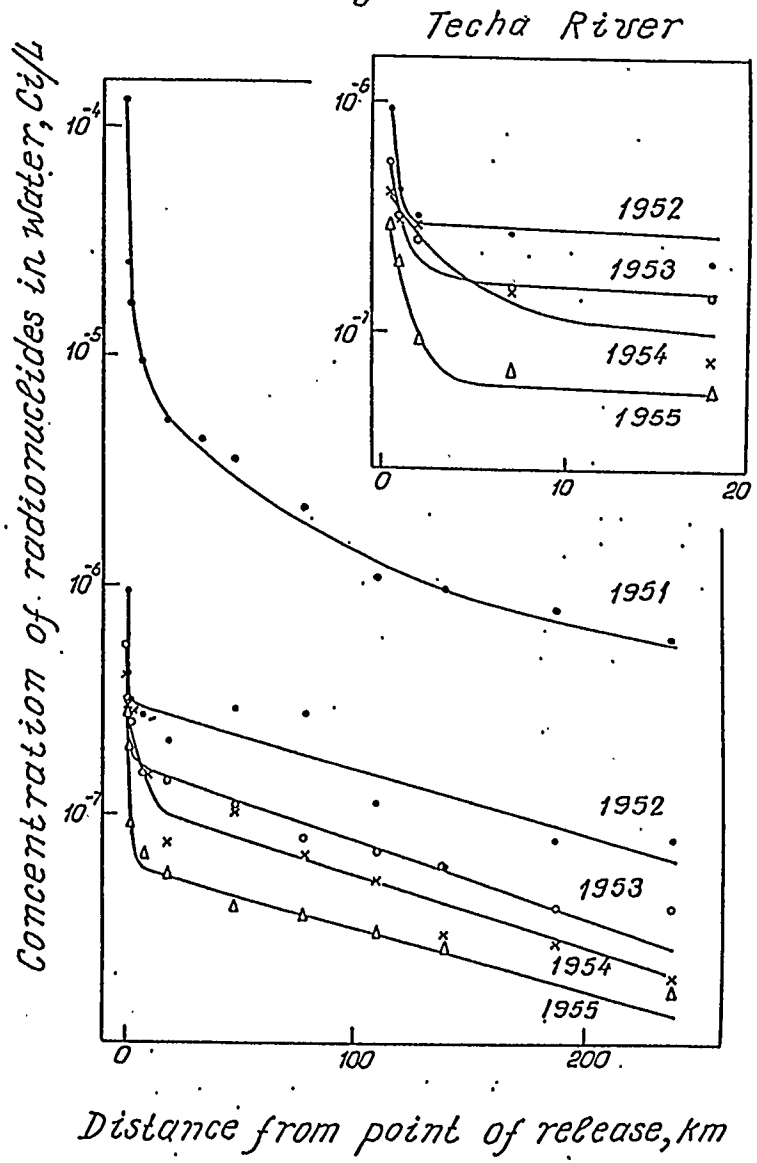

Techa River
Concentration of radionuclides in water, Ci/l
10^{-4}
10^{-5}
10^{-6}
10^{-7}
1951
1952
1953
1954
1955
0
100
200
Distance from point of release, km
10^{-6}
10^{-7}
1952
1953
1954
1955
0
10
20

Fig 3.

Techa River

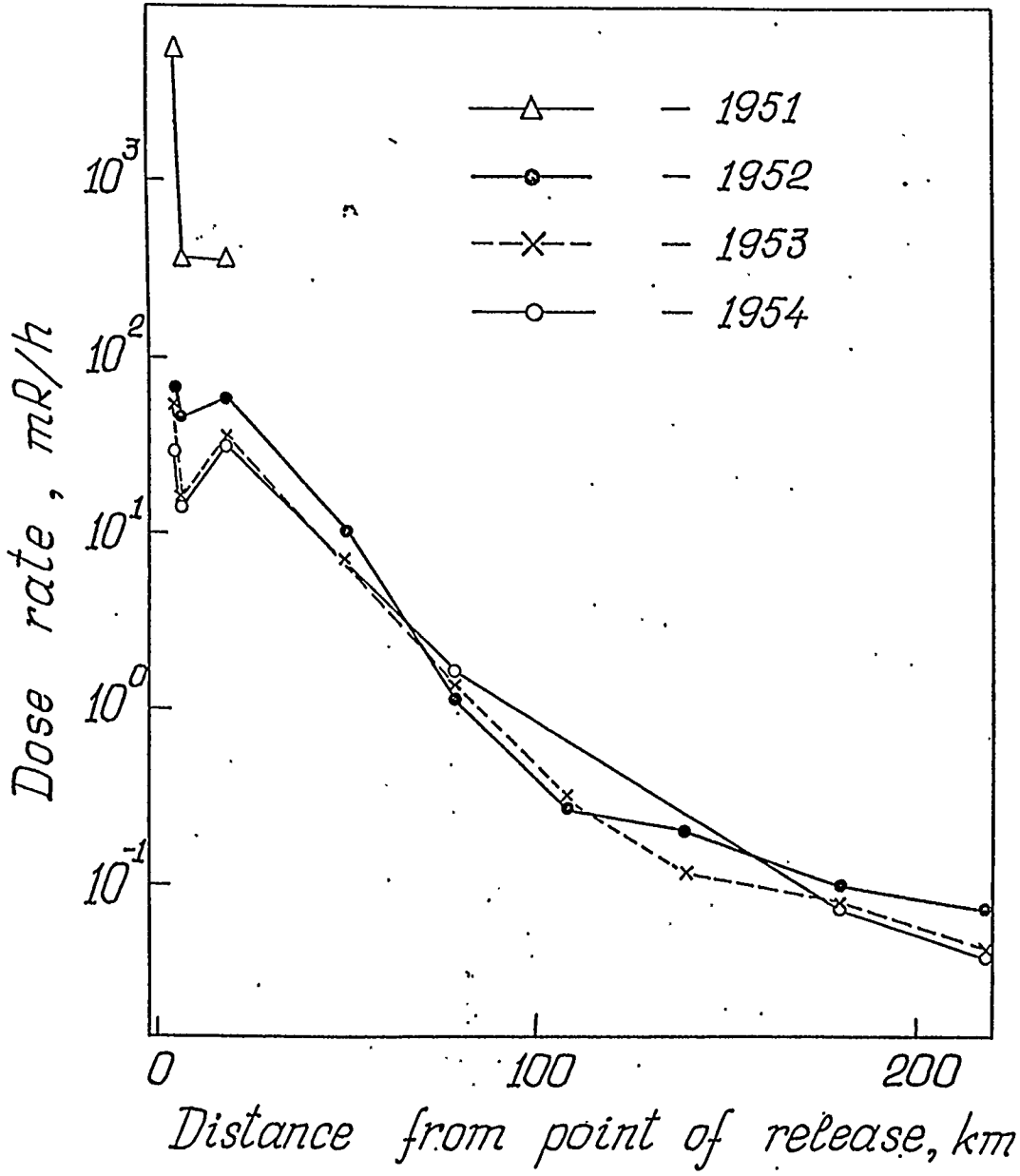


Fig 4.

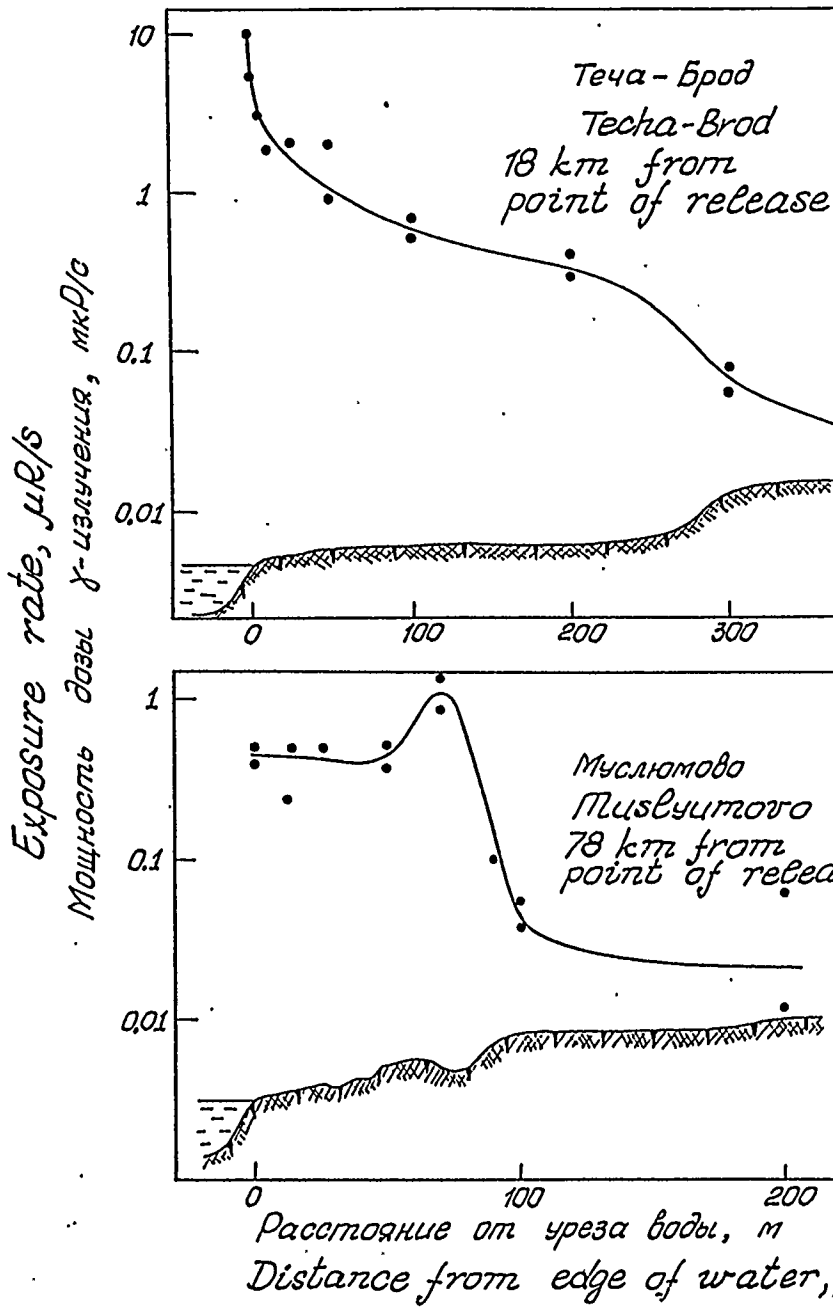


Fig 5.

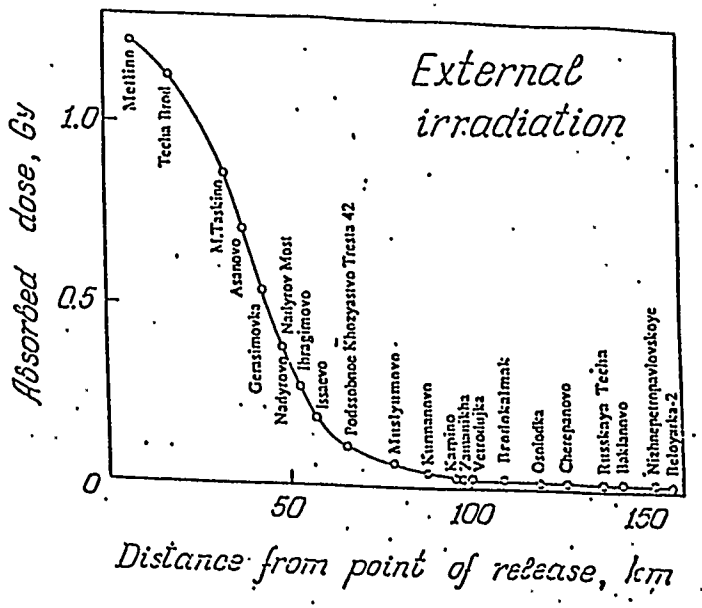


Fig 6

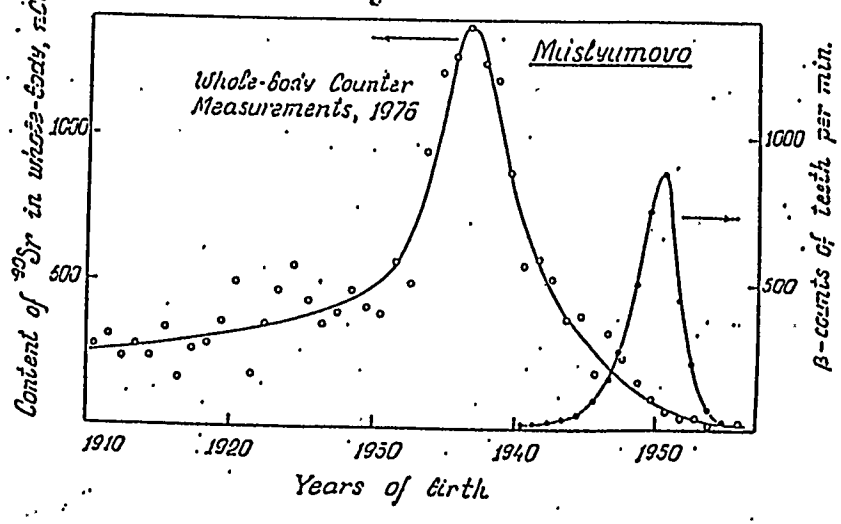


Fig 7.

Musliumovo

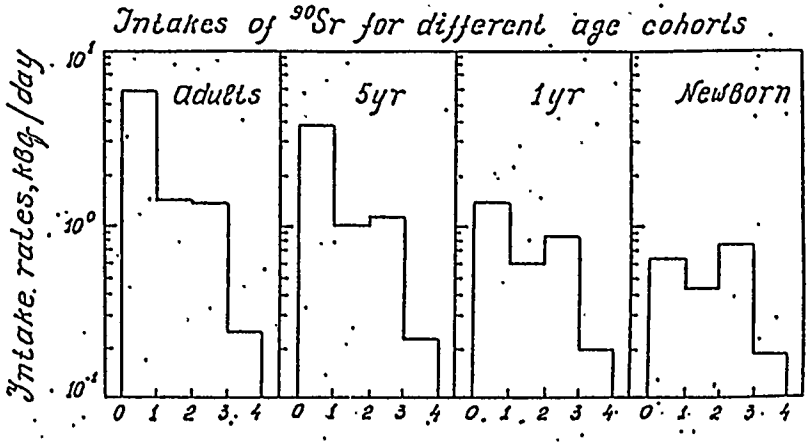


Fig 8.

Musliumovo

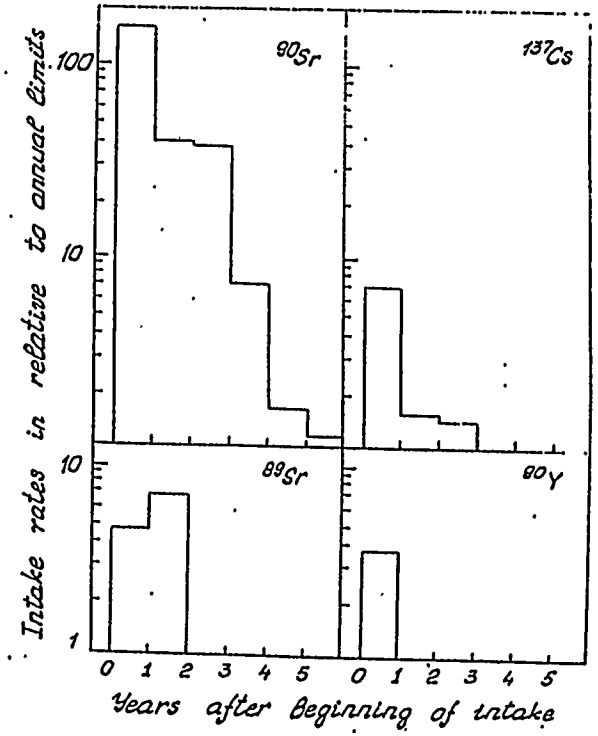


Fig 9.

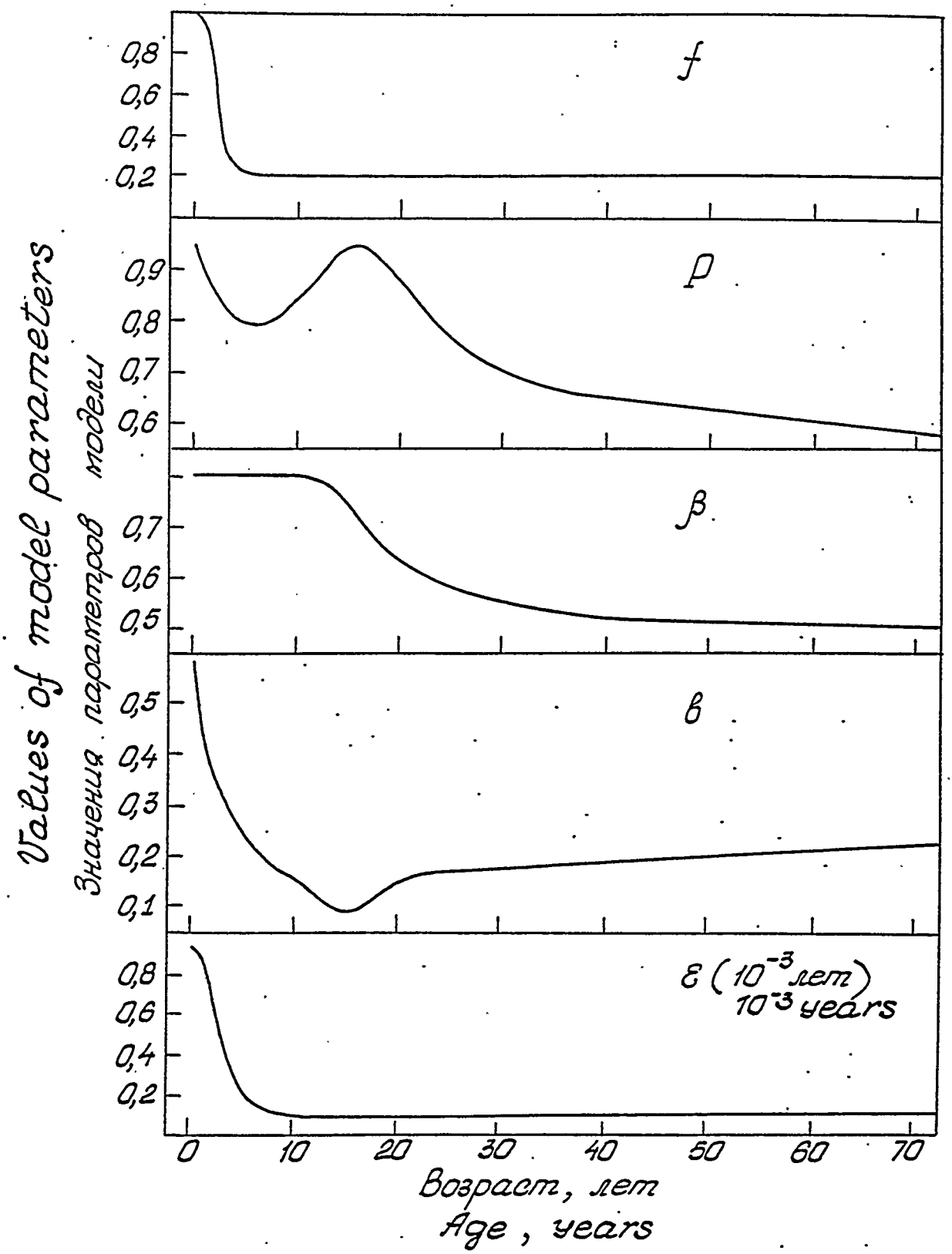
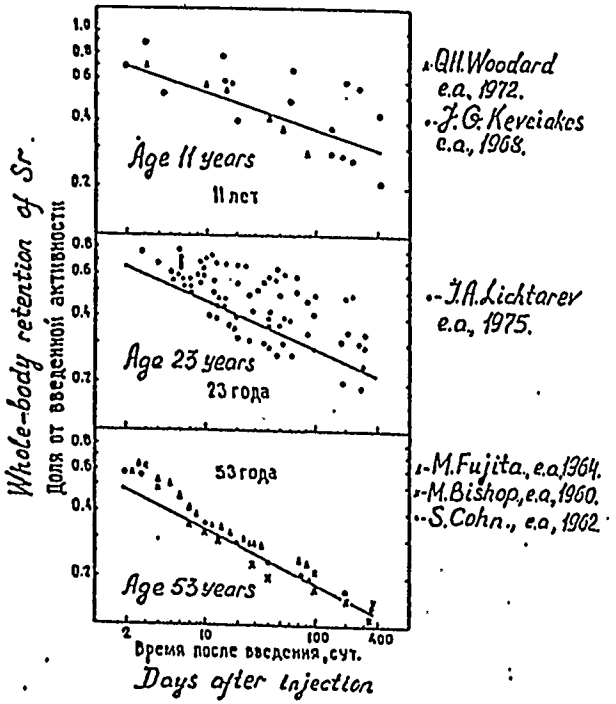
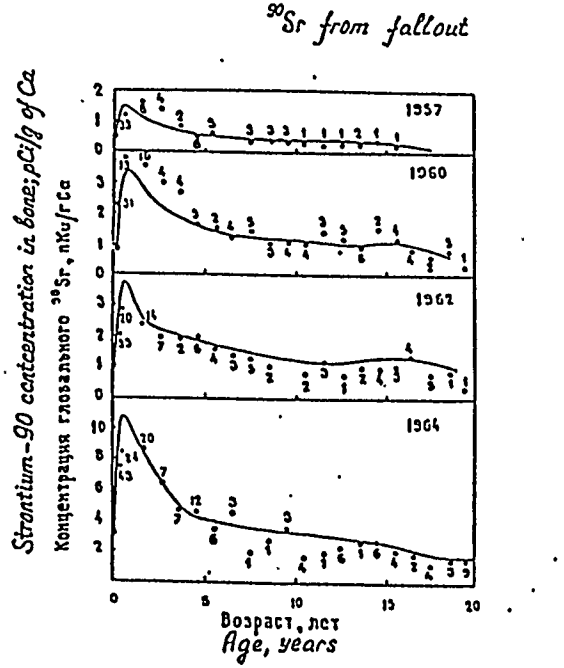

Values of model parameters
Значения параметров модели
f
0,8
0,6
0,4
0,2
p
0,9
0,8
0,7
0,6
β
0,7
0,6
0,5
θ
0,5
0,4
0,3
0,2
0,1
ε (10⁻³ лет)
10⁻³ years
0,8
0,6
0,4
0,2
0
10
20
30
40
50
60
70
Возраст, лет
Age, years

Fig 10



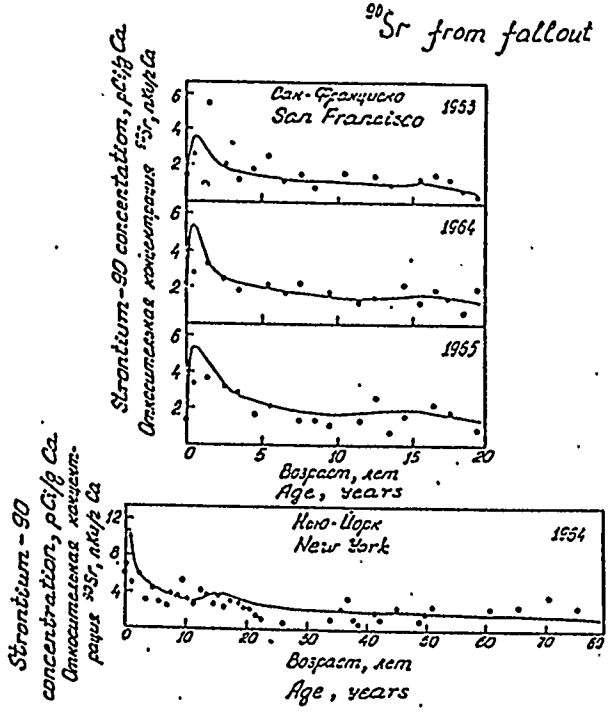
Curves-our model retention functions for different ages-in comparison with the measured Strontium retention.

a



Curves-our model calculations according to "United Kingdom diet, intake levels (D.Popworth e.a.1973). Points-measured levels (redrawn from F.Loutit e.a.1967). Figures beside data points represent the quantities of bone specimens.

b



Curves-our model calculations according to "New-York diet" and "San Francisco diet" intake levels (Leggett R.W. e.a. 1982). Points-measured levels (redrawn from Ibid).

c

Fig 11

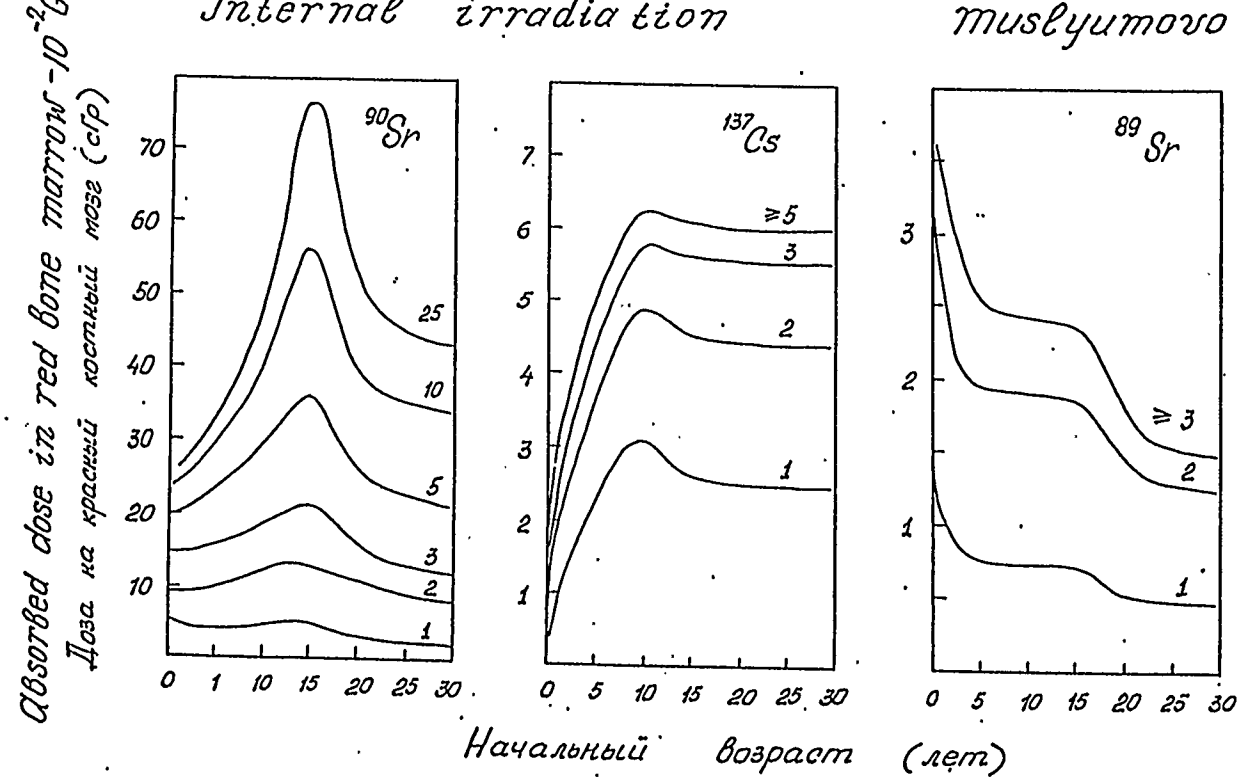

Internal irradiation
Muslyumovo
Absorbed dose in red bone marrow - 10^{-2} Gy
Доза на красный костный мозг (сГр)
^{90}Sr
^{137}Cs
^{89}Sr
25
10
5
3
2
1
≥5
≥3
Начальный возраст (лет)
Initial age, years
Numbers besides curves represent years from beginning of intake

Fig 12.

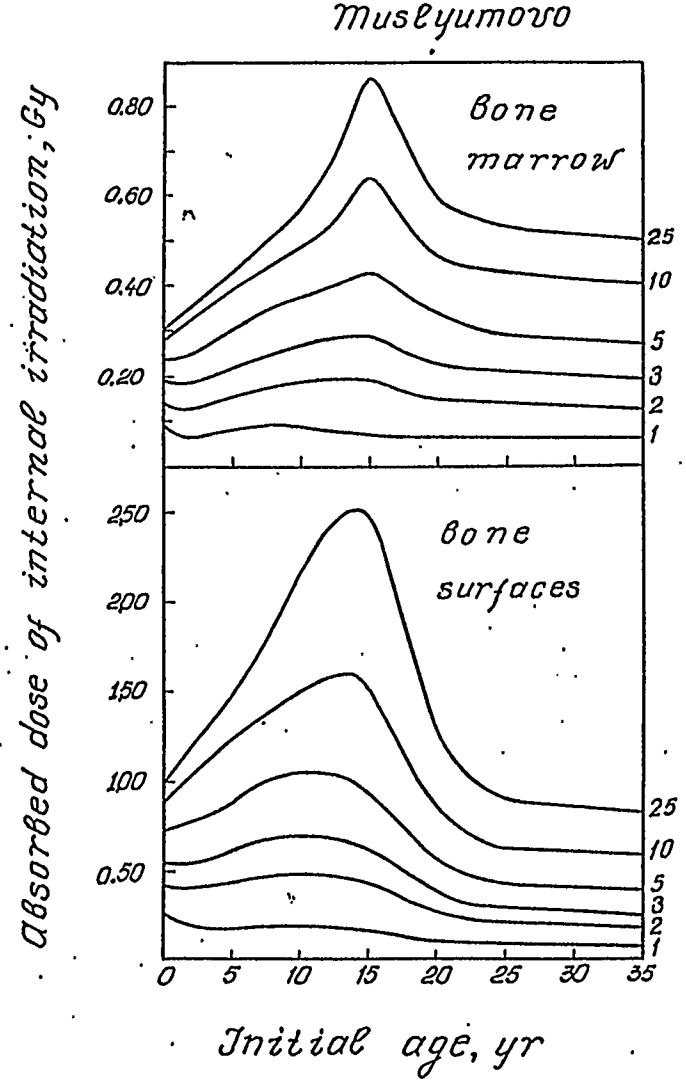

Muslyumovo
Absorbed dose of internal irradiation, Gy
Bone marrow
Bone surfaces
25
10
5
3
2
1
Initial age, yr

Fig 13

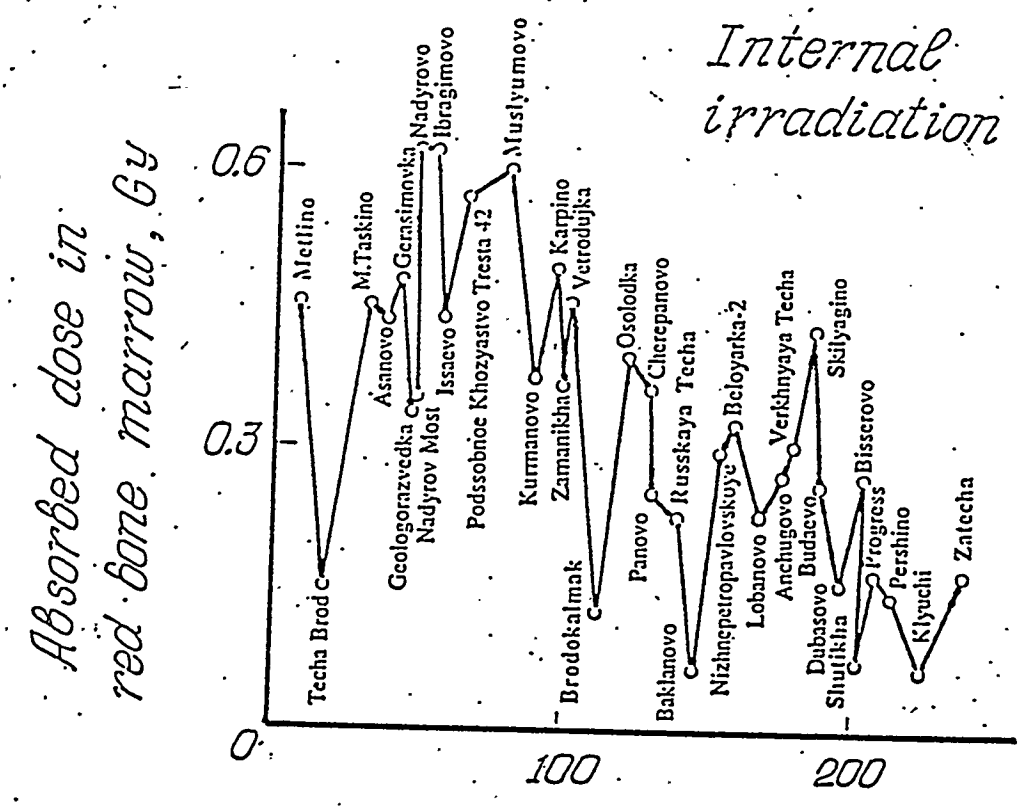
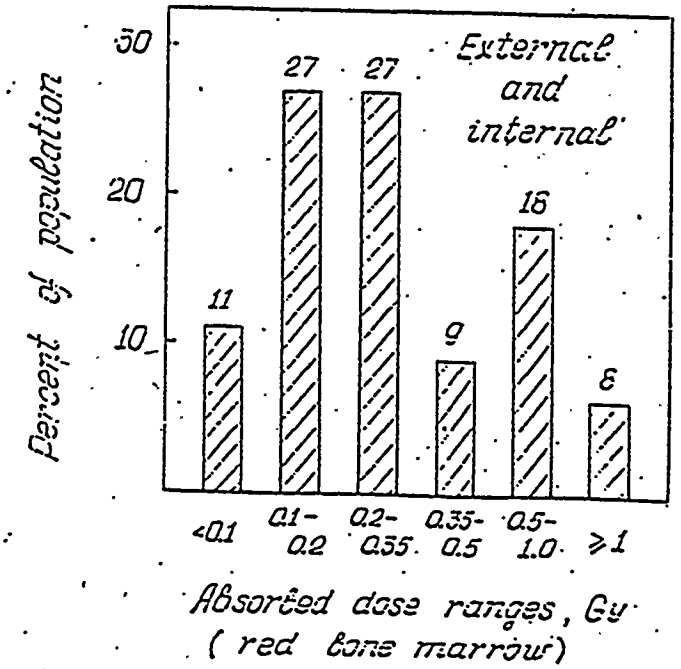

Internal irradiation
Absorbed dose in red bone marrow, Gy
0.6
0.3
0
100
200
Distance from site of release, km
Metlino
Techa Brod
M.Taskino
Asanovo
Geologorazvedka
Nadyrov Most
Gerasimovka
Nadyrovo
Ibragimovo
Issaevo
Podssobnoe Khozyastvo Tresta 42
Muslyumovo
Kurmanovo
Karpino
Zamanilkha
Vetrodujka
Brodokalmak
Osolodka
Cherepanovo
Panovo
Baklanovo
Russkaya Techa
Nizhnepetropavlovskoye
Beloyarka-2
Lobanovo
Anchugovo
Verkhnyaya Techa
Budaevo
Dubasovo
Shutikha
Skilyagino
Bisserovo
Progress
Pershino
Klyuchi
Zatecha

Fig 14.


Percent of population
30
20
10
External and internal
11
27
27
9
16
8
<0.1
0.1-0.2
0.2-0.35
0.35-0.5
0.5-1.0
≥1
Absorbed dose ranges, Gy (red bone marrow)

Radiation Risk and Cancer Mortality in Exposed Populations Living Near the Techa River in Southern Urals

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Urals Research Center for Radiation Center

The appropriateness of applying risk coefficients calculated from short-term exposures at high doses for the assessment of radiation effects at low doses is currently much debated. The problem can be resolved on the basis of the data obtained from a long-term follow-up of the population exposed in the early 1950's, when discharges of radioactive wastes from a radiochemical plant into the Techa River (Southern Urals) occurred [1, 2]. This paper discusses the results of an analysis of cancer mortality during the period 1950-1982.

1. Statistical Analysis of Cancer Mortality

For the purposes of long-term epidemiological studies, the Techa River Registry was established at the former Branch 4 of Biophysics Institute (currently, Urals Research Center for Radiation Medicine). The Registry includes all people who resided in the Techa area at the time the waste discharges were made. The Registry is updated with information about the individuals who were lost to follow-up due to death or migration. If a person has moved to a far-off village, it is sometimes very difficult to obtain information on their health status.

The data on mortality was obtained from the archives of the Civil Registrars' Registries in the Chelyabinsk and Kurgan Regions. Death certificates containing passport information, place of residence, age at death and the basic death cause were retrieved from these archives. The mortality study covered the population of two rural districts of the Chelyabinsk Region (Krasnoarmeysky and Kunashaksky), and one settlement in the Kaslinsky district (before the population was relocated), and two districts in the Kurgan Region (Kataysky and Dolmatovsky), all of which are located on the banks of the Techa. The residents of the contaminated stretches of the river made up 15-25% of the total population of the districts. The information on the death certificates and that of the Registry was compared and, based on this comparison, cohorts of exposed and unexposed people (controls) were established.

According to the Registry the total number of exposed people was

28,210 as of January 2, 1991. In 25,152 cases, the follow-up period was 33 years. For 67.3% of the deceased, the death causes were verified. Of this number, 774 people died of neoplasms.

The followed-up population was heterogeneous in terms of levels of radiation exposure and other carcinogenic factors. As a result of this feature, six almost homogeneous study groups were established (Table 1). It should be noted that a minimum structural unit in the study was defined as a village, the residents of which were assumed to have received equal average doses. The following criteria were used as the basis for grouping the exposed people:

1) distance downstream of the discharge site to the homes which accounted for the dose effect and correlation of external and internal irradiation;

2) forceful evacuation (whether the individual was evacuated or continued to reside on the banks of the Techa). This criterion was used to set up a cohort of residents who are still exposed to doses below the admissible levels defined for population in the document "USSR Norms of Radiation Safety" (5 mSv per year);

3) administrative-territorial division of the region which determines a number of non-radiation factors involved: ethnicity (ethnic features, genetic characteristics, age structure, dietary specificities, etc.), living standards, and health care standards.

The control groups were set up on the basis of only the third criterion, that is, they were matched for non-radiation factors listed above. Table 1 shows the characteristics of the follow-up population groups and cancer mortality rates.

Fig. 1 shows cancer mortality rates versus effective dose equivalent (H_E) and, in Table 2, the results of the regression-correlation analysis are listed. As shown by the totals for all groups, the correlation with doses is not statistically significant; the radiation factor is only responsible for less than half of the overall variance ($\sigma^2_P = 0.42$). As is evident from the controls, the points pertaining to the Tartar-Bashkir population lie much lower than the points describing the Russian population. This necessitates the determination of separate statistical relationships for the Russian and the Tartar cohorts. Table 2 shows that such an approach

resulted in a significant increase in correlation coefficients, moreover, the dose dependence became statistically significant for the Russian cohort.

It is well recognized that ethnic factors govern spontaneous cancer rates to a considerable extent and can also affect radiation risk levels [3]. Therefore, it was considered appropriate to make further assessments separately for the Russian and Tartar populations. However, such differentiation made the analysis of all groups pointless since there are only two groups of Tartars, and the three Russian groups had nearly equal H_E values (Table 1). For this reason, we shall only analyze two large groups of exposed subjects: Group A, consisting of Russians with H_E equal to 0.13 Sv and dose range 0.03-1.40; and Group B, consisting of ethnic Tartars and Bashkirs with average H_E of 0.37 and the dose range 0.15-1.0 Sv.

Two control groups matched for ethnicity and age were analyzed. Table 3 summarizes average doses to specific organs for the exposed groups A and B.

Table 4 shows the data on cancer mortality for both specific organs and the total. Significant differences between groups A and B are observed for the following sites: esophagus, stomach and other organs of the digestive system, uterine body and cervix and other sites. The differences in cancer mortality structure are particularly dramatic. Thus, the incidence of esophagus cancer in Tartars is much higher as compared to the Russians (17.45% and 3.5%, respectively). Among Russians, cancer of the uterine body and cervix occur with higher frequency (12.3% and 7.3%, respectively). The assumption that the foregoing deviations are caused by certain differences in age composition between the Russian and Tartar-Bashkir populations was not confirmed since, after all values were standardized, the difference remained for almost all sites. Thus, the studies of cancer mortality structure confirmed a need to make a separate analysis for groups A and B.

A comparison of the study groups and controls showed that significant differences could be detected for the following sites: uterine body and cervix for group A, cancer of the red bone marrow and lymphatic tissue for group B. It was discovered that there is no trend towards increases in bone cancer: it should be noted that on the Techa the osteogenic cells received very high doses as compared

to all other organs and tissues. It should also be noted that there were deaths from skin cancer, which is considered a curable type of cancer. The incidence of lethal skin cancer is 2-10 times higher in the exposed individuals, particularly among Tartars and Bashkirs.

The absence of any significant differences in cancer incidence for most sites were observed in a relatively small number of cases. However, it should be stressed that of the 13 organ-specific cancer types, slightly higher mortality rates were observed for 11 sites among the exposed in group A, and for 10 sites among the exposed in group B, in comparison with matched controls. In total, there were 89 excess cancer deaths (17% of the expected number) among the exposed Russians over the 33-year follow-up period. The estimate for the Tartar-Bashkir population is 35 (27%).

2. Calculation of Radiation Risk Coefficients

The calculation of radiation risk coefficients requires that an account should be taken of the extensive variability of dose distribution in different organs and tissues, which was the result of a considerable fraction of ^{90}Sr and ^{89}Sr in the radionuclide mixtures ingested.

The disparity in radiation modified the total risk of neoplasms. The concept of effective dose equivalent (H_E) as a unique approach to radiation effect estimation with respect to late effects does not help resolve the problem. The question of additive risk in case of exposure of one or several organs, the role of weighting factors and their dependence on age and sex are still subjects for discussion. All this makes the concept of effective dose equivalent (H_E) which is used for prediction unfit for the task of numerical evaluation of the revealed risk. Therefore, we had to rely on doses absorbed by individual organs and tissues and to consider individually the corresponding tumor sites.

The use of the dose reconstruction technique [4] has convinced us that the estimations of radiation dose to red bone marrow and osteogenic cells are most reliable. For these tissues, the basic dose-forming radionuclide was Sr-90, and absorbed doses were reconstructed on the basis of the measurements of radionuclide content using a unique whole body counter (SICH-9.1). Radiation exposure of these tissues may result in the development of leukemia and bone tumors. As stated above, no increase in bone cancer mortality was observed among either the Russians or the Tartars. The forecast based on the risk coefficients for bone cancer [5] showed that the probability of

detection of at least one excess case in the population (A+B) is equal to 0.45. Therefore, we can establish a "practical threshold" within the range of estimated doses affecting the bone surfaces (<2.3 Gy) and using our statistics (7 cases among the exposed and 54 among the controls) we can establish a "practical threshold".

Estimation of leukemia risk as one of the most important exposure effects on the Techa was made earlier, on the basis of morbidity data [6, 7]. The main result of that research can be summarized as follows: leukemia rates were statistically significant and dependent on the radiation level; an increase is observed 5-20 years after the exposure with predominant types of leukemia being acute leukemia and chronic myeloleukemia; the absolute risk was estimated to be 0.48-1.1 per 10^4 PY Gy, depending on the measurement technique. It is 3-5 times lower than the respective estimates for A-bomb survivors [8]. We assumed that the differences in risk coefficients may be attributed to the radiation conditions; i.e., chronic low doses on the Techa and acute high doses from A-bomb explosions. Since the question of the "reduction factor" (DDREF) of risk coefficient at low dose rates is extremely important, it was decided to re-verify our conclusion with respect to leukemia, applying a different approach to risk estimation.

The estimates of the parameters for linear additive and relative excess risk model were obtained using the AMFIT program, which was created by D. Preston and D. Pierce, RERF, Hiroshima, Japan, for analyzing cohort survival data. Input data for making the estimations are presented in Table 5 and output data in Table 6.

As illustrated by Table 6, absolute risk estimates do not differ from our earlier findings. Now we can speak about statistically confirmed decrease in absolute risk coefficients in comparison with similar assessment for A-bomb survivors. Relative risk estimates have confidence intervals too large to allow definite conclusion.

Apart from red bone marrow, the following cancer sites were chosen for risk evaluation: stomach, esophagus, uterine corpus and cervix, lung and bronchi, and female breast. These sites were selected because they accounted for the highest numbers of cancer deaths. Radiation doses to these organs were mostly due to external gamma-irradiation and exposure to ^{137}Cs uniformly distributed in organs and tissues. Therefore, it was assumed that these organs had received equal average absorbed doses.

Our estimation of risk coefficients was based on the following main assumptions:

1) two alternative risk models were studied: additive (model of absolute risk) and multiplicative (mode of relative risk):

2) it was found that the dependence of risk on dose was linear within the dose range considered. This assumption enabled us to use the following simple formulas for risk estimation:

relative risk coefficient: $$RR = \frac{R-R_O}{R_O D}$$

absolute risk coefficient: $$AR = \frac{R-R_O}{D}$$

Here R is the site-specific cancer mortality rate for exposed group; R_O is a similar parameter for the control group; D represents the average absorbed dose in an organ or tissue in question.

Table 7 lists risk coefficients calculated for 6 main sites on the basis of these formulas. As can be seen from Table 7, ethnic characteristics affect both absolute and relative risk estimates; a higher absolute risk may correspond to a lower relative risk estimate, as was the case with leukemia.

The highest risk was found to be associated with cancer of the uterine body and cervix. However, it should be noted that merging of these two sites into one gradation was dictated by the use of this particular grouping on death certificates. Generally, the uterine body and cervix are considered separately, which made it impossible to find analogous cases for comparison.

Risks for the other five sites were compared with similar results received by other researchers for populations with higher doses [8-10]. As shown in Fig. 2 risk coefficients estimated for different exposure conditions can, in principle, be compared. If the multiplicative model is used, the conclusion about the diminishing leukemia risk coefficient estimated on the basis of the additive risk model is not confirmed.

In order to verify these conclusions, the risks for groups of individuals exposed to intermediate doses to organs in excess of 1 Gy (group 1, Table 1) and the rest of the Russian population exposed to radiation doses lower than 0.5 Gy (group 4.5 and 6, Table 1) were estimated separately. The results of these estimations are listed in Table 8, which can be compared with grouping A-bomb population into "high dose individuals" and "low dose individuals" [3]. As demonstrated by Table 6, no distinct decrease in risk coefficients can be observed for the exposed population, when grouped in this way.

The results contradict the experiment-based conclusion about a decrease in carcinogenic risk per unit dose at low dose rates. The contradiction, however, can be easily explained. In actual accidental situations, people are affected by a number of unfavorable factors; the interaction of such factors may have a stimulating effect on cancer development. Thus, in this case, radiation may not only be cancer-causing agent, but can also act as a factor stimulating (i.e., promoting) insidious cancer-type changes in the organism.

The question of latent period in cancer risk is also very important. In relation to leukemia, the time was estimated on the basis of data on morbidity dynamics [6,7]. The dynamics of leukemia mortality shown in Fig. 3 correspond, in general, to the data. As is shown by the curve describing the irradiated population, there exists a characteristic maximum which is observed late in the second decade after exposure. Toward the end of the follow-up period, the incidence of leukemia among the exposed people decreases to values corresponding to the spontaneous levels.

Fig 4 shows dynamics of mortality from neoplasms in other sites:

1) risk of stomach cancer became realized in both exposed groups within the first two decades of exposure;

2) with respect to lung cancer both exposed groups showed a tendency towards an increase in risk level at the end of the follow-up period;

3) with respect to "ethnic cancer" the risk was found to exceed the estimates for controls in any period of the follow-up;

4) insufficient statistical data did not allow any conclusions to be drawn about the dynamics of breast cancer.

In general, it should be emphasized that excess incidence of cancers in all sites were observed among the exposed people in the first decade of the exposure. Since the time of risk realization is of great importance, it was considered expedient to conduct additional studies of the total cancer mortality (Fig. 5). Figure 5 shows that curves describing the Russian and Tartar-Bashkir populations are similar in shape. This is the result of improved diagnostic practices, aging of the followed-up population, and a worldwide tendency to an increase in cancer incidence. A distinct difference should be noted between the exposed and non-exposed populations in the 1950's. Early in the 1980's, a dramatic trend towards increased cancer incidence among exposed cohorts was observed.

This conclusion is not surprising in respect to well established theories suggesting that the risk of radiation-induced cancer persists throughout the lifetime and even increases with age, as is confirmed by the relative risk model. The excess of malignancies during the first decade after exposure does not correlate with the established idea that the latent period for radiogenic solid cancers is estimated as approximately 10 years. This, however, confirms our earlier proposition that radiation exposure may stimulate the development of neoplasms from cells that have undergone carcinogenic transformation. This may occur as a result of immune system obliteration. The phenomenon can be proved indirectly on the basis of an analysis of overall mortality: a high mortality was noted in the 1950's for exposed elderly people, mostly from cancer; and children, from diseases of digestive system and respiratory organs. Thus the weakest age groups of the population were most affected.

Without any doubt, this assumption calls for further proof. It is imperative that the studies of the Techa populations be continued, and a detailed analysis of cancer mortality for the population exposed due to the Kyshtym accident be made. The results obtained thus far enable us to use "the dose and dose rate effectiveness factor" (DDREF) for very tentative predictions of late effects in populations exposed to radiation accidents.

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Legends to the Figures

Fig. 1. Cancer mortality rate depending on the effective dose equivalent for the groups of Russian and Tartar-Bashkir population and the regression line for the whole population (1), Russian (2), and Tartar-Bashkir (3) populations (Pearson's correlation coefficients P_p=0.65, 0.86 and 0.98 respectively).

Fig. 2. The comparison of the relative and absolute risk coefficients for leukemia (a), stomach cancer (b), lung cancer (c), esophagus cancer (d), estimated for the Russian (1), and Tartar-Bashkir (2) population of the Techa River; for the ATB Survivors in Hiroshima and Nagasaki (3); for patients treated for ancylosing spondylitis (4), and for cervical cancer (5).

Fig. 3. Dynamics of leukemia mortality for whole Techa River Population in comparison with nonexposed population of the same districts.

Fig. 4. Dynamics of site specific cancer mortality for the Russian (group A) and Tartar-Bashkir (group B) population. Closed dots = exposed people; open dots = control groups. The numbers of cancer deaths are shown above the dots.

Fig. 5. Dynamics of total cancer mortality for the Russian (group A) and Tarter-Bashkir (group B) population. Closed dots = exposed people; open dots = control groups. The numbers of cancer deaths are shown above the dots.

Table 1

Characteristics of the Observed Cohort and Mortality from Malignacies

Groups under observation	Duration residence on the bank strip of the Techa	Predominant nationality	Average effective dose equivalent, Sv	Number of person years under observation	Number of case of death from cancer	Cancer mortality rate per 10^5 person years	90% confidence intervals
1	5-8 years	Russians	1.40	13065	35	268	187-372
2	9-10 years	Tartars and bashkirs	0.52	50627	84	166	132-205
3	live permanently	Tartars and bashkirs	0.24	61850	79	128	101-159
4	10-12 years	Russians	0.11	35250	76	216	170-271
5	live permanently	Russians	0.075	129980	274	211	186-237
6	live permanently	Russians	0.074	131303	226	172	150-196
Group of comparoson 1 (in regard to exposed groups 2 and 3)	-	Tartars and bashkirs	-	372320	425	114	103-126
Group of comparoson 2 (in regard to exposed groups 1,4,5)	-	Russians	-	828050	1467	177	168-187
Group of comparoson 3 (in regard to exposed groups 6)	-	Russians	-	938010	1513	161	153-169

Table 2

Results of Correlation-regression Analysis of Relationship Between Cancer Mortality Rate per 10^4 person years (Y) and H_E in Sv(X)

	Total population	Russians	Tartars and bashkirs
Pearson Correlation Coefficient ρ_P	0.65	0.86*	0.98**
Spirman rank correlation coefficient ρ_S	0.33	0.90*	1.0**
Parameters of regression equation $Y = A + BX$			
A (per 10^4 person years)	16.1	18.3	11.0
B (10^{-4} person years/Sv)	6.7	6.2	10.1

Note: * – significantly confirmed $P<0.05$;

** – significance is not determined from low number of points

Table 3

Average Absorbed Doses in Organs and Effective Dose Equivalents for Exposed Groups A and B

Groups	Absorbed dose in organ, Gy			Effective dose equivalent, Sv
	Red Bone marrow	Bone surfaces	Soft tissues	
A	0.25	0.50	0.09	0.13
B	0.70	1.45	0.25	0.37

Table 4.

Structure of cancer mortality

Site of Tumours	Group A				Group B			
	Exposed		Control		Exposed		Control	
	number of cases	10^{-5} person years	number of cases	10^{-5} person years	number of cases	10^{-5} person years	number of cases	10^{-5} person years
All neoplasms including:	611	197	2980	169	163	145	425	114
Oral cancer and pharynx cancer	12	3.9	50	2.8	3	2.7	2	0.5
Oesophagus	13	4.2	103	5.8	30	26.7	74	19.9
Stomach	104	59.4	1010	57.2	44	39.1	122	32.8
Other organs of gastro-intestinal tract	76	24.5	371	21.0	19	16.9	54	14.5
Respiratory organs	98	31.7	499	28.3	21	18.7	72	19.3
Bone	7	2.3	47	2.7	0	<0.9	7	1.9
Skin	8	2.6	24	1.4	4	3.6	0	<0.3
Female breast	10	3.2	47	2.7	3	2.7	8	2.2
Uterine corpus and cervix	98	31.7	367	20.8	17	15.1	31	8.3
Other urinogenital organs	38	12.3	173	9.8	7	6.2	25	6.7
Leukaemia	19	6.1	64	3.6	8	7.1	6	1.6
Other neoplasms of lymphatic and hemopoietic tissues	10	3.2	34	1.3	2	1.8	3	0.8
Other and not specified tumours	38	12.3	191	10.8	5	4.4	21	5.6

The comparison of exposed individuals with control groups showed that authentic differences could be traced in the following sites: in group A – uterine corpus and cervix; in group B – neoplasms in red bone marrow and in lymphatic tissue. One can notice the absence of any trend of the increase in bone cancer (one should not forget that in the situation on the Techa osteogenic cells

Table 5.

Leukaemia Mortality in Techa River Study

Dose group	Mean RBM dose, Gy	Nationality 1-Russian 2-Tartar	Person-years under observation	Cases of leukaemia
1	0	1	938013	34
2	0	1	828050	30
3	0	2	372320	6
4	0.176	1	131303	5
5	0.18	1	129980	9
6	0.29	1	35256	3
7	0.61	2	61850	4
8	0.82	2	50627	4
9	1.64	1	13063	2

Table 6.

Leukemia Risk Coefficients Estimated with the Help of AMFIT Program

Cohort observed	Excess absolute risk per 10^4 PY Gy	Excess relative risk per 1 Gy
Total population	0.75 (0.13-1.36)	2.24 (0.21-4.27)
	0.85 (0.24-1.45)*	3.24 (0.48-6.00)*
Russian only	0.93 (-0.1-1.96)	2.55 (-0.48-5.76)
Tatar and bashkir	0.80 (0.06-1.54)	4.97 (-1.83-11.8)

Note: * - Stratification on "nationality" factor.

Table 7

Evaluation of Excess Absolute and Relative Risk Made on the basis of the Cancer Mortality Rate among the Population on the Techa River.

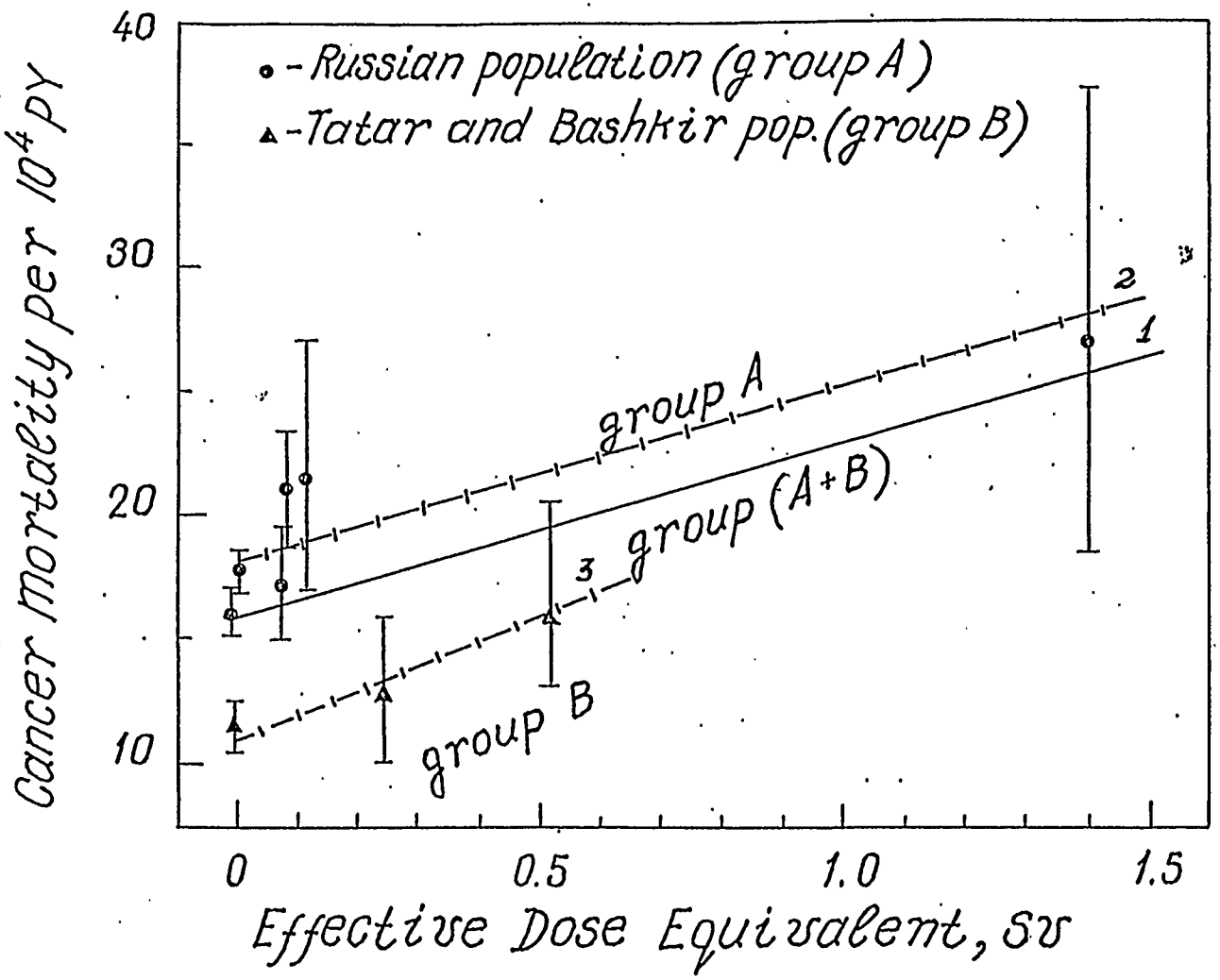
Localization	Absolute risk per 10^4 PY Gy		Relative risk per Gy	
	group A	group B	group A	group B
Leukaemia	1.0	0.79	2.8	4.9
Stomach	2.4	2.5	0.43	0.76
Female breast	9.6	0.21	2.4	0.97
Uterine corpus and cervix	12.6	2.7	5.8	3.3
Lung and bronhus	3.8	<0	1.3	<0
Oesophagus	<0	2.7	<0	1.4

Table 8

Estimation of Relative Risk Values per 1 Gy Absorbed Dose by the Organ for Different Dose Ranges

Site of neoplasms	the Techa river (Russians)		Hiroshima and Nagasaki	
	>1 Gy	< 0.5 Gy	>0.5 Gy	<0.5 Gy
Leukaemia	1.98	3.05	5.53	2.44
Stomach	0.15	0.79	0.26	0.45
Lung	0.43	2.38	0.60	1.06
Female breast	-0.77	6.67	1.21	0.82

Fig 1.


40
30
20
10
0
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1.0
1.5
Cancer mortality per 10^4 PY
Effective Dose Equivalent, Sv
• - Russian population (group A)
▲ - Tatar and Bashkir pop. (group B)
group A
group (A+B)
group B
1
2
3

Fig 2.

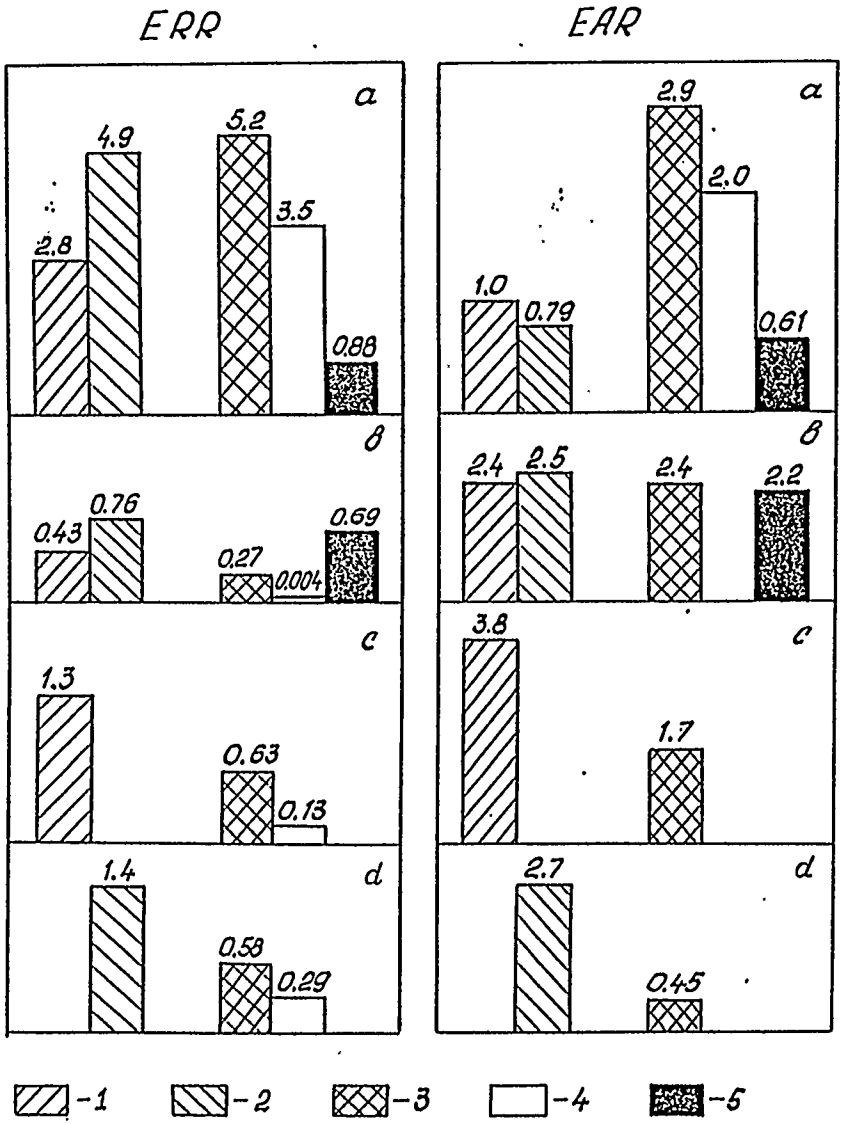
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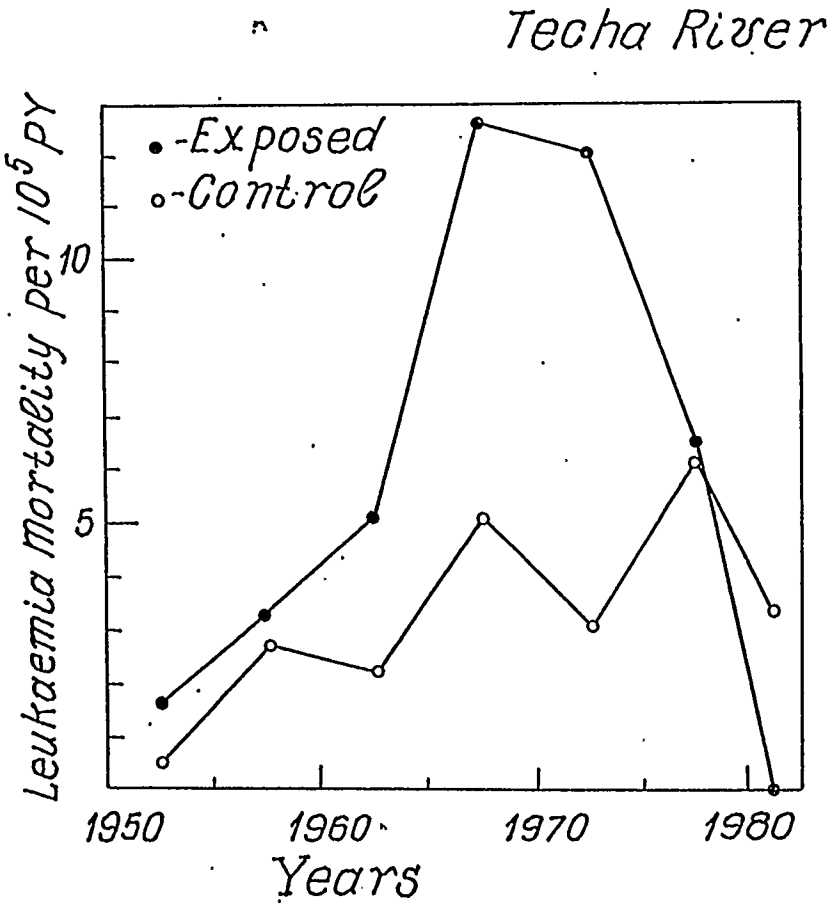
Fig 3.


Techa River
•-Exposed
∘-Control
Leukaemia Mortality per 10^5 PY
10
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1950
1960
1970
1980
Years

Fig 4.

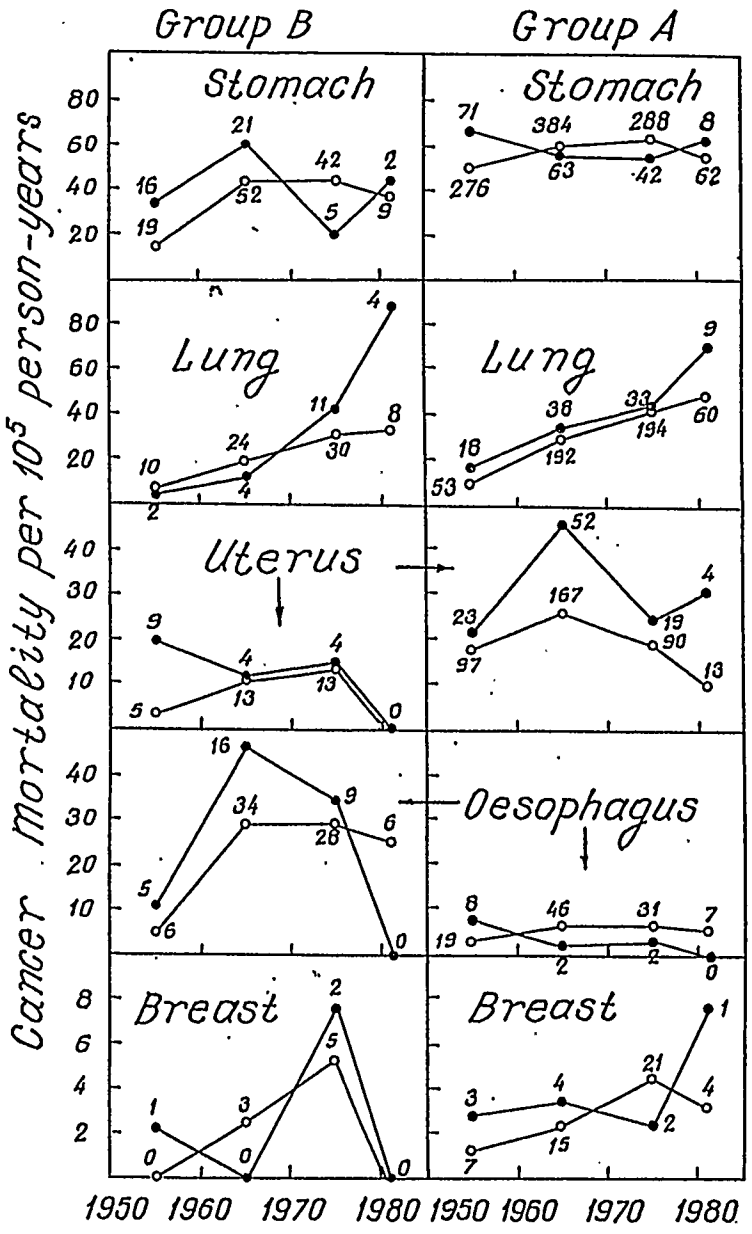
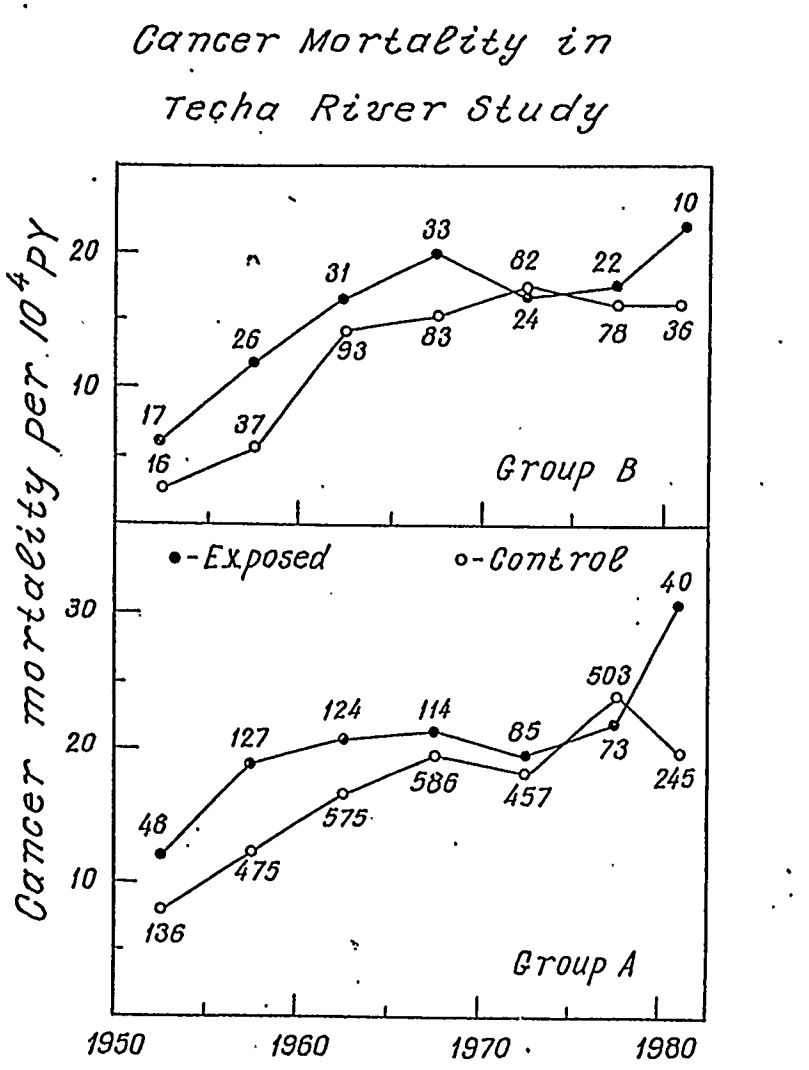


Fig 5



The number of cancers are given above the circles

Mortality from Malignant Tumors in Hematopoiotic and Lymphatic Tissues Among Personnel of the First Nuclear Production Complex in the USSR

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ABSTRACT

This paper reports on results from the study of haemo-lymphoblostosis (HLB) mortality among personnel of the first nuclear materials production complex in the USSR.

Two registers have been made which include all personnel at the reactor facility (register A) and a radioreprocessing facility (register B), divided in to those who started to work during 1948–72 (period of hire 1948–53–cohort 1; period of hire 1954–59–cohort 2). The most important contributor to harmful occupational effects was external γ-radiation. During the first years, adverse radiation situations were observed at both facilities, which resulted in significant overexposure of personnel.

All cancer mortality rates and leukemic proportion of the cancer mortality levels were significantly increased only in the men of I cohort, facility B. A statistically significant excess of standardized leukemia mortality rates above national normal data and of actual leukemia mortality over the expected level was also found in this cohort (1 B). The actual mortality excess over the expected in this cohort accounted for the increase in acute leukemia mortality reported for the period of 1953-60, i.e. in 3–12 years after the initial radiation contact. Relative risk of leukemia for A-bomb survivors at the age ATB of 20 and older is reported as 3.92 per Gy (Shimisu et al. 1987), and is 2.8 times higher than the risk shown in our study (3.92:1.4–2.8).

Epidemiological studies of nuclear facility workers can provide important data on cancerogenic risk estimation and radiation significance for cancer

induction (Gilbert et al. 1989; Beral et al. 1988; Nikipelov et al. 1990). However, these studies have a number of positive and negative features, which must be considered during the data interpretation. Positive features include: sufficiently precise quantitative estimates of individual doses; very uniform working and living conditions and medical care; good safe keeping of personnel medical and other archived documents useful for dose reconstruction through the specification of previous occupational duties, individual disease histories, bad habits (eg. smoking), and other factors, which can be significant for oncogenesis. Negative features include: a comparatively small population of workers; the lack of adequate controls; and a possible "healthy worker effect" related to strict medical selection of people for nuclear plants.

We took these features into account in our studies of cancer mortality and used the continuous method of follow-up of fixed personnel cohorts, considering every human follow-up from the initial occupation at this plant up to his death (for those individuals alive up to 1 January, 1990). Thus, a sufficiently large number of follow-up person-years provides for a potential increased significance of results.

We analyzed common, age-specific and standardized mortality rates; the standardization and estimation of expected fatal cases is based upon age-specific coefficients of cancer mortality among the adults in the former USSR averaged over 1970-86 (Mal. tum. in the USSR, 1989; USSR population, 1987). We used national rather than regional statistics, as the workers were recruited from all over the country. The specification of the relationships with working conditions and investigation of dose dependence is based upon the internal control and comparative groups differed in dose, occupation duration, initial time of radiation contact and analysis of age-standardized mortality rates. Sex-standardization is not used, as men and women's mortality are analyzed separately.

The current report includes the data on mortality from malignant tumors in hematopoietic and lymphatic tissues (hemolymphoblestosises-HLB) in a cohort of men started to work at the first soviet nuclear complex in 1948–53. A cohort of men started to work at the same complex in 1954–58 was used as a comparative group.

The first nuclear complex in the USSR included an atomic production reactor (Facility A, commissioned in June 1948) and a radioreprocessing plant for plutonium isolation from exposed fuel (Facility B, commissioned in December, 1948). During the first years, adverse radiation situations were observed at both facilities (Nikipelov et al. 1990) which resulted in

significant overexposure of personnel (Table 1; Figures 1, 2). The most important dose contributor to occupational harmful effects was external γ-radiation. Data on individual γ-doses was obtained from safety plant services. Individual film badge dosimeters photocontrol techniques (IPCL) were employed from the first months of plant operation. An individual dose measurement error is ± 20%. These procedures included a calibration of every film batch using a reference γ-radiation source with the error of ± 10%.

We developed registers, which include all personnel from both facilities who began work between 1948–72. Register A comprises data on 4550 persons and register B, 7800. At present, we can document the follow-up of 83–85% persons included in both registers.

Table 2 represents characteristics of the first two cohorts. At the beginning of working activities at the plant, more than 80% of the men were less than 30 years old. Therefore, at present, the largest number of older persons and, respectively, the highest percent of deaths appear in the first cohort; i.e., among those who started to work before 1953 (inclusive). In the second cohort, mortality amounted to less than 20% among men and in subsequent cohorts 10–11% among men and 7–9% among women. This accounted for the choice of the cohort to be studied for the total cancer mortality and fatal hemo-lymphoblastosises. Analysis of fatal cancer rates (Table 3) showed significant increases in mortality from malignant tumors only in the men of cohort 1, facility B. The difference between cancer mortality structures in both cohorts at both facilities (Table 4) and national average data is unessential.

The hemo-lymphoblastosis (HLB) proportion was a bit higher, but significant differences in this class of tumors also appeared only in cohort 1 of Facility B. The actual HLB mortality exceeded the expected cases in both cohorts at both facilities (Table 5), but statistically significant excesses of standardized rates over the national average data and actual mortality over the expected was also found only in cohort 1, facility B. HLB mortality in 1 cohort, facility B was higher than in I cohort, facility A and cohort 2, facility B. Accordingly, analysis of HLB mortality in cohort 1, facility B was more detailed. The actual mortality excess over the expected in this cohort accounted for the increase in acute leukemia mortality for the period 1953–60; i.e., in 3–12 years after the beginning of radiation contact. Sixteen fatal acute leukemias appeared among 25 cases of HLB, including 14 cases from M_1 –M_3 types and 2 cases from M_6. Four chronic myeloid leukemias and 5 malignant

lymphomas, including 1 lymphograulomatosis were observed among individuals.

Twelve acute leukemias from 16 appeared in 3–11 years after the beginning of radiation contact. External γ-doses at early acute leukemias were very high total–562.3± 83.2cGy; per year–374.3± 63.0 cGy) and were significantly higher than in cases with prolonged latency (total–297.0± 37.1 cGy, per year–155.3± 54.8 cGy). Rather similar morphological features of myeloproliferative process, similar latent period, high radiation doses (both total and per year) provide for the assumption of radiation-induced acute leukemias.

Estimated risk of leukemia mortality among men in cohort 1, facility B is represented in Table 6.

Absolute, relative and attributable risk of acute leukemia mortality either did not differ, or was lower than risk coefficients estimated for A-bomb survivors (Shimisu et al. 1987). Excess relative risk of leukemia mortality for persons over 20 years old due to chronic occupational exposure is 2.8 times lower than the risk from a single acute exposure. These data suggest that the dose rate reduction factor, even for high chronic exposures, will be three or more.

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Table 1. General Data on Exposure (External γ-Irradiation According to Individual Photocontrol Data) at the First Industrial Atomic Installations

		Period of Hire			
Facility	Personnel Dose Level	1949-53	1954-58	1959-63	1964-68
A	Average individual dose to all personnel (cGy/y)	32.6±12.6	6.4±1.0	2.5±0.25	2.2±0.6
	Persons exposed to higher than 100 cGy/y (%)	6.5	0.15		
B	Average individual dose to all personnel (cGy/y)	70.4±15.9	17.2±2.0	10.5±2.2	2.4±0.4
	Persons exposed to higher than 100 cGy/y (%)	22.8	0.1		

* For facility A, doses are averaged over 1948-53, as this facility was put into operation in June, 1948, and facility B only in December, 1948.

Table 2. General Data on Personnel Number and Composition in the Register of the First Industrial Atomic Installations (Cohorts 1 and 2)

Cohorts	Rates	Facility A		Facility B	
		Sex			
		M	W	M	W
Cohort 1 (occupation beginning 1948(49) - 1953)	General number of people with known destiny	1422	541	1871	1129
	Number of persons with IPCL data	1286	396	1812	1057
	Total deaths	410	62	618	119
	Deaths percent	31.9	15.6	34.1	11.2
	Number (percent) of people with IPCL data and beginning of occupation at less than age 30	1010 (78.5)	345 (87.1)	1473 (81.3)	944 (89.3)
Cohort 2 (occupation beginning 1954-1958)	General number of people with known destiny	533	148	1516	245
	Number of persons with IPCL data	509	122	1478	240
	Including deaths from all reasons	96	12	272	19
	Deaths percent	18.9	9.8	18.5	7.9
	Number (percent) of people with IPCL data and beginning of occupation at less than age 30	444 (87.2)	99 (81.1)	1334 (90.2)	199 (82.9)

IPCL - individual photocontrol of an external γ-dose level.

Table 3. Cancer Mortality Rates Among Men Beginning Work at Industrial Reactors and Radioprocessing Installations Before 1959

Rates	Facility A		Facility B	
	Cohort 1	Cohort 2	Cohort 1	Cohort 2
Number of people	1286	509	1812	1478
Number of person-years of follow-up	45947	15730	61649	44464
Tumor mortality:				
-actual	101	19	197	55
-expected	126.4	26.3	153.2	61.3
Actual versus expected	0.80 (0.6-1.03)	0.72 (0.4-1.28)	1.28* (1.05-1.57)	0.9 (0.6-1.29)
True cancer mortality rate (cases per 10^5 person-years)	219.89±	120.8±	319.6±**	123.7±
Standardized cancer mortality rate (cases per 105 person-years)	205.8± 21.1	186.2± 34.4	331.6±*** 23.1	231.9± 22.7
Average individual cumulative γ-dose (cGy)	122.1±2.4	49.2±1.1	245.3±3.21	71.6±1.3

* Differencies between actual and expected deaths are significant
** Significantly higher than at Facility A
*** Significantly higher than among adult men in USSR with cancer mortality averaged over 1970-86 and amounted to 257.62 cases per 10^5 persons-years

Table 4. Cancer Mortality Structure (% Among Men) Facility A and B Workers

Tumor localization (ICD-9 Code)	Facility A		Facility B		USSR (1970-1986)
	Cohort 1	Cohort 2	Cohort 1	Cohort 2	
Mouth, lips, throat (140-149)	3.0±1.7	-	0.5±0.5	-	3.4
Esophagus (150)	2.0±1.4	-	1.0±0.7	5.5±3.0	4.3
Stomach (151)	32.7±4.7	21.0±9.3	20.3±2.9	14.6±4.8	20.5
Rectum (154)	4.9±2.1	5.3±5.1	5.1±1.6	3.6±2.5	4.1
Other digestive organs (153,155-159)	9.9±3.0	10.5±7.0	11.7±2.3	10.9±4.2	12.2
Larynx (161)	3.0±1.7	5.3±5.1	2.0±1.0	3.6±2.5	3.5
Trachea, bronchi, lung (162)	22.8±4.2	36.8±11.1	32.5±3.3	30.9±6.2	31.4
Prostate (185)	3.0±1.7	-	3.6±1.3	1.8±1.8	2.8
Urinary organs (188, 189)	5.9±2.3	5.3±5.1	4.1±1.4	7.3±3.5	5.1
Lymphatic and hematopoiotic tissues (200 - 208)	5.9±2.3	10.5±7.0	12.7±2.4*	10.9±4.2	5.4
All other localizations (160, 163, 170-173, 186, 187, 190-199)	6.9±2.5	5.3±5.1	7.1±1.8	10.9±4.2	7.3

* Significantly higher than at Object A and in the USSR, $p \leq 0.05$

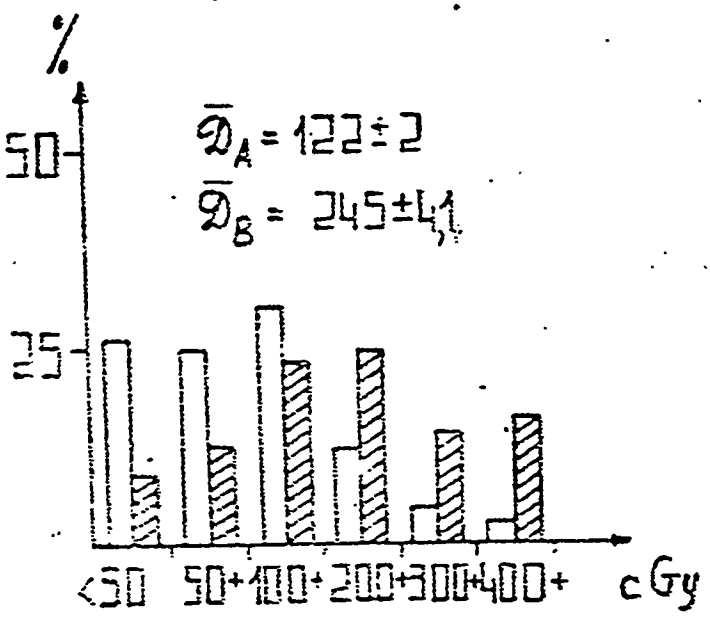
Table 5. Hemo-lymphoblastosis Mortality Among Personnel (Men) at Object A and B Started to work in 1948-53 and 1954-58 (Cohorts 1 and 2, Respectively)

Rates	Object A		Object B	
	Cohort 1	Cohort 2	Cohort 1	Cohort 2
Number of men with IPCL data	1286	509	1812	1478
Observed deaths	6	2	25	6
Expected deaths	5.68	1.41	7.11	3.59
Actual versus expected (95% confidence level)	1.056 (0.34-3.3)	1.42 (0.16-12.2)	3.52* (1.54-8.09)	1.67 (0.45-6.15)
True mortality rate (cases per 10^5 pers.-years)	13.1±5.3	12.7±9.0	40.6±8.1*	13.5±5.5
Standardized rate (cases per 10^5 pers.-years)	9.4±4.3	12.6±8.9	31.3±7.1**	14.9±5.8

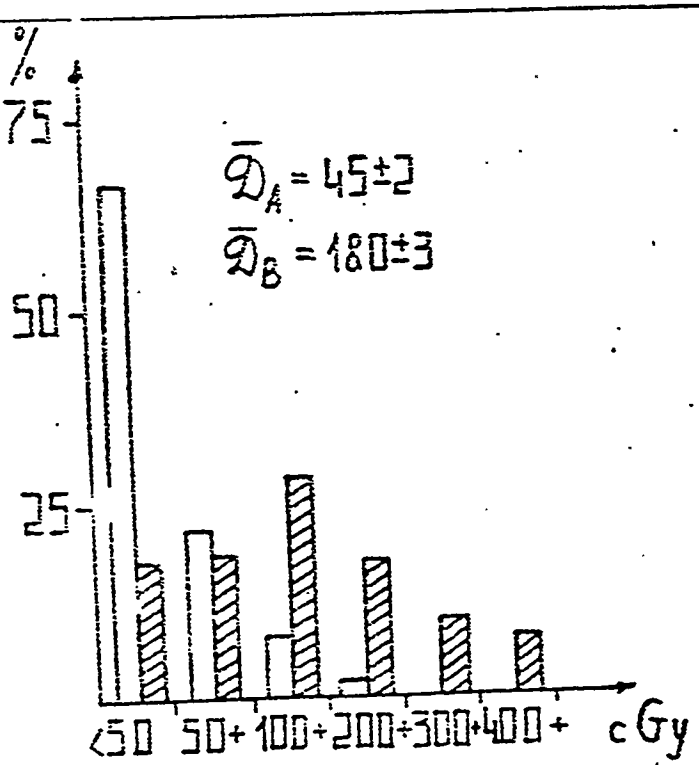
* Significantly higher than in Cohort 2 at Facility B
** Significantly higher than in Cohort 1 at Facility A

Table 6. Risk Estimates for Leukemia, Based on Workers of Facility B (Cohort 1) for 40 Years of Follow-up

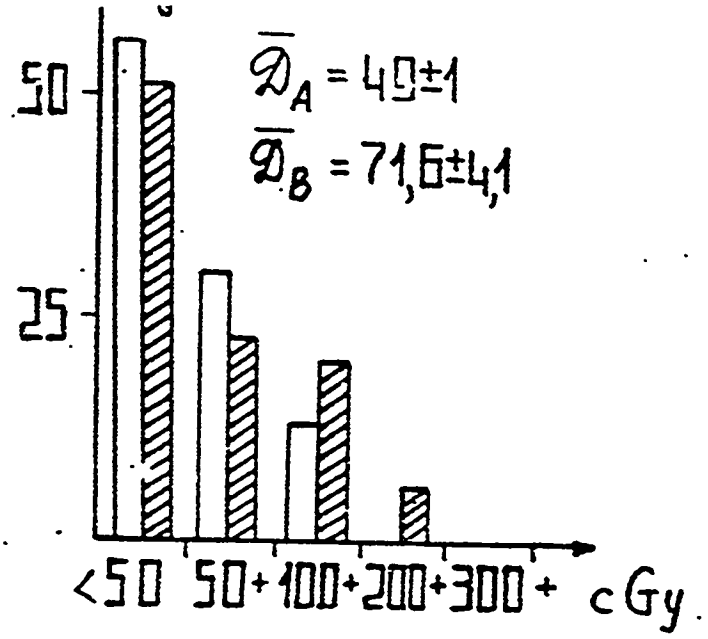
	Facility B (Cohort 1)	Lss-Cohort Age ATB20+
Average individual cumulative dose M±m (Gy)	2.45±0.03	
Age-standardized mortality rate (deaths per 10^5 person-years)	25.0±6.4	
Spontaneous mortality rate (deaths per 10^5 persons per year)	5.5	
Absolute risk (excess deaths per 10^5 person-years-Gy)	7.96	
Excess relative risk (per Gy)	1.4	3.92
Attributable risk (%)	78	
Coefficient of prolongation of dose	3.92:1.4=2.8	



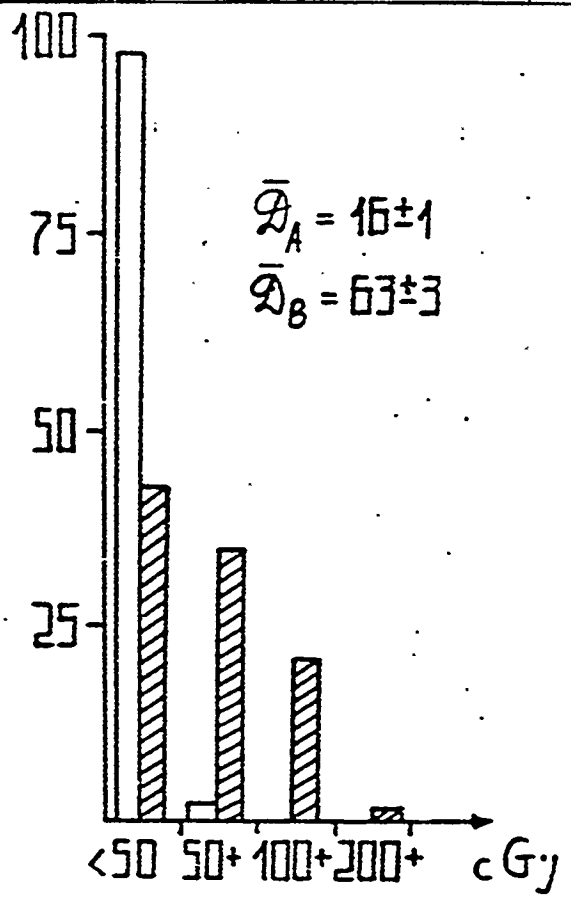
Distribution of the personnel of the plants A and B by cumulative dose of external whole body γ-irradiation. Men, cohort I (period of hire 1949-53). □ - A ▨ B



Distribution of the personnel of the plants A and B by cumulative dose of external whole body γ-irradiation. Women, cohort I (period of hire 1949-53) □-A ▨-B



Distribution of the personnel of the plants A and B by cumulative dose of external whole body γ-irradiation. Men, cohort II (period of hire 1954-58)



Distribution of the personnel of the plants A and B by cumulative dose of external whole body γ-irradiation. Women, cohort II (period of hire 1954-58)

□ - A
▨ - B

Research Initiatives in Ionizing Radiation Research
United States Department of Energy
Office of Epidemiology and Health Surveillance

Michael E. Ginevan
Deputy Director

OEHS PRESENTATION TO "STOCHASTIC WORKSHOP", JUNE 17, 1992

Main Points

1. DOE/DHHS Memo of Understanding and the future of major epidemiologic studies.
2. Dose reconstruction at DOE Sites.
3. RERF: Current Status
4. Internal Emitters Studies.
5. Development of the CEDR database
6. Biostatistical Studies

The DOE/DHHS Memo of Understanding

Administration:

1. **CDC is Lead DHHS Agency; Worker studies are in NIOSH.**

2. **A MOU implementation task force will implement transfer of research to CDC/NIOSH and will coordinate DOE/DHHS interactions thereafter.**

3. **Transition period through FY 1992.**

4. **Joint research agenda. Oversight by ESHAC (Environment Safety and Health Advisory Committee).**

5. **Intramural and Extramural Research; Extramural is competitive peer review.**

The DOE/DHHS Memo of Understanding
(continued)

Projects to be transferred:

1. Health and Mortality Study of DOE Contractor Workers

2. Offsite Radiation Dose Reconstructions
   A. Hanford (HEDR)
   B. Feed Materials Production Center (Fernald)

New Activities for FY 1992

1. Offsite Dose Reconstructions
   A. Savannah River Site
   B. Idaho Falls National Engineering Laboratory

2. Childhood leukemia: Replicate Gardner study.

Fernald Dosimetry Reconstruction Project (FDRP)

Purpose:provide an independent analysis of radioactive releases from the Feed Materials Production Center (FMPC) and to reconstruct doses to the population living near FMPC.

Management: CDC via MOU with DOE. Contract awarded to Radiological Assessments Corporation (John Till) in July 1990.

Six tasks in project:

1. **Identify all points of radionuclide release to environment going back to facility opening in 1951. Report published in January 1991.**
2. **Determination of source terms for facilities at FMPC. Report published December 1991.**
3. **Source term uncertainty analysis.**
4. **Environmental pathway analysis using results of Tasks 2 and 3.**
5. **Verification and validation of transport models.**
6. **Estimation of radiation doses to public.**

RERF: AREAS OF ACTIVITIES IN 1992-1993

1. Continue the follow-up of the survivors of the atomic bombs to assess the late health effects of radiation (much of the population is reaching ages where cancer risk is high).

2. Initiation of efforts to study outcomes other than cancer (mental retardation, cardiovascular effects, osteoporosis).

3. Initiation of molecular studies to relate changes in immunocompetence to the genetic constitution of exposed individuals and to relate these findings to cancer outcomes.

4. Expand studies of the genetic changes in children due to parental exposures.

5. New worldwide emphasis on training of physicians in the care of persons exposed to low-doses of radiation.

Internal Emitter Studies

1. **Main Study: Radium Dial Painters (ANL)**

2. **<u>Not</u> transferred to DHHS.**

3. **Study will continue through FY 1992 at present level.**

4. **Emphasis is on data analysis as opposed to collection.**

CEDR:The Comprehensive Epidemiologic Data Resource

1. Two Phases:
   A. Pre-CEDR: prototype software - is complete now.
   B. CEDR: Final system: design and implementation begins in 1993.

2. Data in Pre-CEDR now.
   A. Analysis files for all completed DOE health and mortality epidemiologic studies.
   B. Preliminary metadata for analysis files.
   C. IARC data files.
   D. Metadata for IARC files
   E. Intermediate files for DOE Health and Mortality Studies

CEDR: continued

3. Data to be added to CEDR

   A. Improved metadata generated by user interactions.
   B. Atomic bomb survivor data from RERF.
   C. Cross-sectional data from PAREP databases.
   D. The Radium Dial Painters data.
   E? The U.S. Navy Nuclear Shipyard Workers data.
   F. Selected data from the DOE/CDC environmental dose reconstructions.
   G? Data from the Utah fallout studies.
   H? Data on U.S. Commercial Nuclear Workers.
   I. Data from future HHS epidemiologic studies. (DOE-HHS MOU).
   J. Access to the Retrospective Epidemiologic Data Inventory System (REDIS; A four year 3.5 million dollar inventory of epidemiologically relevant data at DOE sites)

Biostatistical Studies

Purpose: Identify biostatistical issues which affect conclusions drawn from epidemiologic data, and develop improved methodology for the analysis of epidemiologic data.

1. Methodologic issues
   - A. How do errors in dosimetry affect modeling?
     - i. Bias.
     - ii. Random error.
     - iii. Time dependent errors.
   - B. How does the choice of analytic method influence conclusions drawn?
     - i. Proportional hazards applied when hazards are not proportional.
     - ii. Mechanistic models applied when information is insufficient.
     - iii. The role of a Bayesian perspective.
   - C. Animal to human extrapolation.

2. Data issues
   - A. Can you test for bad data?
   - B. Is it possible to correct errors in dose to improve precision of estimates?

Radiation Dose, Reproductive History, and Breast Cancer Risk Among Japanese A-Bomb Survivors

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INTRODUCTION

Excess risk of female breast cancer is among the most comprehensively documented late effects of exposure to substantial doses of ionizing radiation, based on studies of medically irradiated populations and the survivors of the atomic bombings of Hiroshima and Nagasaki, Japan. In virtually all populations studied, there is a marked dose response, with excess risk approximately proportional to breast tissue dose. Level of response depends strongly upon age at exposure, with the highest dose-specific relative risks observed among women exposed as children or adolescents, and the lowest among women who were over 40 years of age. Remarkably, analyses in parallel of incidence data from the A-bomb survivors and from medically-irradiated patient populations in the United States have found similar excess rates at similar radiation dose levels, exposure ages, and length of follow-up, despite 3 to 5-fold differences in age-specific population rates between the two countries, and correspondingly dissimilar relative risks (Land et al., JNCI 65:353, Preston et al., in preparation).

Relatively little is known about the joint effects of radiation dose with other breast cancer risk factors. An implication of the above-mentioned parallel analyses is that the radiation dose and whatever causes the marked difference between Japanese and American baseline rates are roughly additive in effect. On the other hand, baseline rates increase with age in all populations and, in the major study populations, the excess risk following exposure at any particular age appears to increase over time in rough proportion to age-specific baseline rates; this suggests a multiplicative relationship between dose and the risk factors responsible for variation by age at observation for risk. No fully successful investigation has been done, however, of the interaction of dose with those epidemiological factors, like age at first full-term pregnancy and family history of breast cancer, most closely

associated with risk in epidemiological studies of non-irradiated populations.

METHODS AND MATERIALS

A case-control interview study of 201 living breast cancer cases and 580 matched controls (2-4 per case, depending upon radiation dose), drawn from a defined cohort of Japanese A-bomb survivors, was conducted to identify epidemiological variables strongly related to risk and to investigate their interactive relationships with radiation dose. A non-standard design was used, in which radiation dose was one of the matching variables; the others were age ATB (at the time of the bombings) and city. Analyses for main effects were straightforward, whereas the interaction analysis relied upon information about radiation dose effects from a concurrent incidence study of the entire cohort. At the time of case and control selection, the T65D dosimetry system was in effect (seed Jablon, this proceedings). The change to the DS86 system resulted in no gross mismatches, since the correlation between DS86 and T65D breast tissue dose is over 90%, but there was some loss of cases and controls for whom DS86 doses had not be calculated.

The interaction analysis was focused on discriminating between additive and multiplicative interaction models in the linear scale. If the excess, dose-related risk is aD where aD denotes radiation dose to breast tissue and the unknown parameter may depend upon age ATB, and if X denotes another risk factor (e.g., number of births), then the general interaction model

$$RR(D, X) = (1+aD)(1+bX)+gX \quad (1)$$

has the additive model as one special case ($b = 0$) and the multiplicative model as another ($g = 0$). An Alternative general model is a geometric mixture of the additive and multiplicative models,

$$RR(D, X) = \{(1 + aD)(1 + bX)\}^{q}\{1 + aD + bX\}^{1-0}; \quad (2)$$

here, the additive model corresponds to $q = 0$ and the multiplicative model to $q = 1$. Matching on D precludes estimating a from the case-control data, and therefore a cohort-based estimate must be used when estimating the other parameters with the additive model or either general model; with the multiplicative model the estimate of b is independent of dose.

The only reason for not matching on *D* in a conventional design is to permit estimation of a from the case-control data. If we know a exactly (the limiting case as the size, and numbers of baseline and radiation-induced cases, of the study cohort are allowed to increase without limit) matching on *D* would be more efficient because it would increase the amount of case-control study information for estimating b and g. By the same reasoning, matching on dose should be advantageous whenever there is a cohort-based estimate of a, provided only that it is no worse than the estimate obtainable from an unmatched design (that condition should always be true for a nested design). The degree of advantage depends upon the uncertainty of the cohort estimate for a.

Since the cohort data have no information about X, the cohort and dose-matched case-control data sets are virtually orthogonal with respect to the dependence of risk on *D* and X, provided that *D* and X are uncorrelated. Thus, for estimation of parameters in an additive or mixed model, the problem of adjusting for uncertainty in a is essentially similar to that of adjusting for error in an independent regression variable. In terms of hypotheses testing, error in a (and in *D*) should reduce power for testing the null hypotheses of multiplicativity against the additive alternative. Tests of the additive null vs. the multiplicative alternative should be biased towards rejection if a is overestimated, and should be conservative if a is underestimated. Thus if, as expected, random error in *D* leads to underestimation of a, the result should be conservative for these tests. On the other hand, bias against the additive null would result if the actual, as opposed to estimated, dose tended to be higher for cases than for their matched controls (the same bias affects an unmatched design). A sensitivity analysis based on the general model (2) found that, for these data, discrimination between the two models depended little upon whether the upper or lower 95% confidence limit for a was used.

RESULTS: MAIN EFFECTS ANALYSIS

The main effects analysis used linear logistic models, in which radiation dose was either ignored or included to adjust for inexact matching with respect to dose. Statistically significant associations with risk were found mainly for reproductive history variables. Age at menarche and age at menopause, however, were not significantly associated with risk, although in other populations such associations have been found. Variables related to parity, age

at first birth, and lactation were strongly predictive of risk. Many strong pairwise correlations were found between variables, but three emerged that were strongly associated with risk and at least partially independent of each other, and which together expressed most of the association of risk with reproductive history. These variables, whose associations with risk are summarized in Table 1, were (1) age at first full-term pregnancy, with age 30 assigned to subjects who had never had a full-term pregnancy, (2) number of births, and (3) cumulative months of lactation. Number of births was statistically significant after adjustment for age at first full-term pregnancy, but not after adjustment for cumulative lactation. Each of the three variables was similarly associated with risk of premenopausal and postmenopausal cancer.

Although it has been reported (Sawada, ABCC TR 34-59) that many survivors stopped menstruating for an extended period after the bombings, there was no difference between cases and controls in the occurrence of amenorrhea either before or after the bombings, nor was there a case-control difference in the reported length of post-bomb amenorrhea. Medical treatment for menstrual problems in general was positively associated with postmenopausal breast cancer risk, as was history of uterine or ovarian surgery prior to cancer diagnosis. The latter finding is difficult to explain, as it is contrary to the results of other studies (but see Shun-Zhang et al., Cancer Res.. 50:5017), and further investigation is needed. The only other medical risk factor to emerge was Quetelet index (weight divided by height-squared) at age 50, which was associated with risk after age 55.

Reported cases of breast cancer in a mother, sister, or daughter were markedly fewer than would be expected according to population rates, and no association with risk was found. These findings probably indicate a failure of the study to identify most cases of familial breast cancer, rather than a lack of association with risk; it would appear that many of the cases in this population were not well informed about their own breast cancer diagnoses (most reported instances of benign breast disease in the cases coincided with their cancers), and it seems likely that the subjects were generally not well informed about instances of cancer in their close relatives.

RESULTS: INTERACTIONS WITH RADIATION DOSE

Deviance-based likelihood ratio tests based on the general model (1) rejected additivity with dose for each of the three reproductive history variables in Table 1 (Table 2). Similar comparisons were inconclusive for other variables associated with risk. Such evidence as there is against the multiplicative model for the three variables suggest even greater deviation from the additive model than predicted by the multiplicative model. That is, women who, because of their reproductive histories, were at an increased or decreased risk of breast cancer in the absence of radiation exposure were at proportionally (or greater) increased or decreased risk of radiation-induced cancer, if exposed. This is illustrated in Figure 1 for cumulative months of lactation: in the left-hand panel, the solid polygonal line, with error bars, corresponds to dose-specific estimates of the odds ratio at one month, 1 + b, for the multiplicative model $RR = (1 + aD)((1 + bX)$. If that model is true, the estimates should all be the same, whereas if the additive model is true the dose-specific estimate of b (which is negative here) should decrease in absolute value with increasing dose, in inverse proportion of $1 + aD$. In fact, the dose-specific estimates and the additive model predictions are on opposite sides of the multiplicative model predictions. Thus the additive model prediction disagrees with "the data" even more than it differs from the multiplicative model estimate. The whole exercise is repeated with the same result in the left-hand panel, but in terms of 1 + g in the additive model $RR = 1 + aD + gX$; there the additive model predictions correspond to a horizontal line, and the multiplicative model predictions to a line with negative slope (g, which is negative in this case, should be directly proportional to $1 + aD$).

DISCUSSION

The purposes of this study were, first, to identify epidemiological factors strongly associated with breast cancer risk among Japanese A-bomb survivors, and to clarify and quantify those associations. Given the strong dose-response relationship for radiation-induced breast cancer in this population, the second purpose was to investigate interactions between dose and other factors so identified. Concerning the first goal, it is important to place the main effects results in the context of findings from a large number of epidemiological investigations of breast cancer in other populations. The most important risk factor in most studies, age at first full-term pregnancy, was a strong risk factor in the present study, as was, independently, lactation history.

This study differed from many others in that no association was found with age at menarche or age at menopause. It is possible that errors in recall may have been partly responsible for these findings, although most subjects interviewed appeared to be confident of their ability to recall age at menarche, in particular, and independent confirmation from clinical records of age at menopause was obtained for most cases and many controls. In an earlier case-control study based on the LSS population, Nakamura (RERF TR 9-77) obtained a nonsignificant relative risk before age 50 of 2.8 for menarche at age 13 or younger. For risk after 50, two-thirds of Nakamura's cases, but only one-fourth of controls, who had experienced natural menopause had stopped menstruating before reaching age 50 (RR = 5.5, p = .027), a result opposite to that usually found. The risk of radiation-induced breast cancer has not depended only upon the amount of radiation dose and the age at which exposure took place. According to the study findings, women who would be considered at increased risk in the absence of such exposure, on the basis of age at first full-term pregnancy, number of births, or cumulative period of lactation, probably should also be considered to be at proportionally increased risk of radiation-induced breast cancer. That much follows from the rejection of the additive interaction model, and the finding that, if anything, departures from the multiplicative interaction model are in the direction of even greater excess risks of radiation-related breast cancer among women with, for example, a late age at first full-term pregnancy.

It is far from a foregone conclusion that the multiplicative interaction model should hold, or that risk factors associated with increased breast cancer risk in non-irradiated women should also be associated with enhanced carcinogenic effects of exposure to ionizing radiation. Women in North America have 3-5 times as much risk as Japanese women, depending upon age, yet the dose-specific, absolute (as opposed to relative) risk of radiation-induced breast cancer does not seem to be any greater among North American women exposed to medical x ray than among Japanese women exposed to gamma rays form the atomic bombs. Apparently, whatever causes American women to be at higher risk than Japanese women interacts approximately additively with radiation does. On the other hand, excess relative risks appear to be fairly constant over time following radiation exposure (Land, J. Chron. Dis., Suppl. 40(2):45S, Tokunaga et al., submitted for publication); apparently, whatever causes baseline breast cancer risk to increase with age

interacts multiplicatively with radiation dose. Thus, both models seem to describe aspects of breast cancer risk following radiation exposure.

Table 1. Odds ratio multipliers per unit increment, with 90% confidence intervals, before (on diagonal) and after (off diagonal) adjustment for other variables.

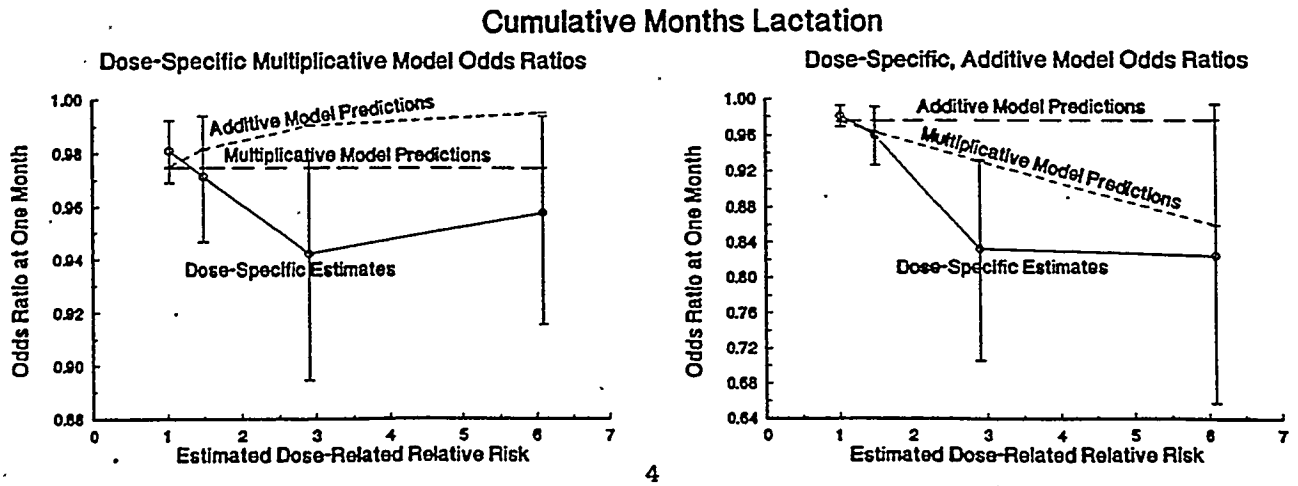
Variable	Adjusted for:		
	Age 1st FTP	No. births	Cum. Lact.
Age 1st full-term preg.	1.08 (1.05 - 1.12)****	1.05 (1.00 - 1.10)*	1.05 (1.01 - 1.10)*
No. births	0.87 (0.78 - 0.97)**	0.81 (0.74 - 0.88)****	0.92 (0.79 - 1.06)
Cum. months lactation	0.987 (0.977 - 0.996)**	0.986 (0.974 - 0.999)*	0.980 (0.972 - 0.988)****

*Two-sided p value $< .10$; ** $p < .05$; **** $p < .0001$.

Table 2. Summary of likelihood ratio test results for the additive and multiplicative models for interaction with radiation dose. Model: $RR(X,D) = (1 + \alpha D)(1 + \beta X) + \gamma X$, where X is the variable of interest and D is radiation dose. Note α is estimated from cohort data, and may depend upon age at exposure.

Variable	Test of Additivity ($\beta = 0$)		Test of Multiplicativity ($\gamma = 0$)	
	Deviance	p	Deviance	p
Age at 1st full-term pregnancy	6.50	.011	1.50	.22
Number of births	5.99	.014	2.47	.12
Cumulative months lactation	7.68	.0056	2.21	.14

Figure 1. Model-specific comparisons between estimated global and dose-specific odds-ratio estimates for cumulative months of lactation, evaluated at one month. Left-hand panel: if the additive model is true, dose-specific estimates of β for the multiplicative model, $RR = (1+\alpha D)(1+\beta X)$, should vary in inverse proportion to $1+\alpha D$. Right-hand panel: if the multiplicative model is true, dose-specific estimates of γ for the additive model, $RR = 1 + \alpha D + \gamma X$, should vary in direct proportion to $1+\alpha D$.



Analysis of the Pace University Center for Environmental Legal Studies Report of September 1990 Entitled "Environmental Costs of Electricity" by R. L. Ottinger, D.R. Wooley, N.A. Robinson, D.R. Hodas, and S.E. Babb

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The purpose of this report is to consider the use made by Pace University in its September 1990 report entitled "Environmental Costs of Electricity"[1] (hereafter cited as the Pace Report) of data from pages 379-381 of the U.S. Department of Energy (DOE) 1987 report entitled "Health and Environmental Consequences of the Chernobyl Nuclear Power Plant Accident"[2] (hereafter cited as the DOE Chernobyl Report).

The statement is made on page 381 of the Pace Report that the DOE Chernobyl Report projected 28,000 fatal cancers from Chernobyl releases that are additional to the 600 million deaths from non-radiological causes in the 3.5 billion persons in the Northern Hemisphere. This statement is not entirely complete: the background incidence of fatal cancers in this population may have both radiological and non-radiological origins; moreover, the additional fatal cancer expectation from the Chernobyl incident is given in the DOE Chernobyl Report as a range from 28,000 fatalities down to zero. In the 1988 paper in *Science* by Anspaugh, Catlin and Goldman,[3], the senior authors of the DOE Chernobyl Report, the number of additional fatal cancers attributable to the Chernobyl incident in the 2.9 billion (corrected from 3.5 billion) persons in the Northern Hemisphere was revised downward to a range of zero to 17,400 fatalities, due in large measure to improved dose distribution data that had just become available. Of these projected 17,400 additional fatal cancers, 6,500 (or about 37%) were projected to occur in the USSR, both estimates ranging to zero.

Based on the revised dose-response relationships given in the 1990 BEIR V Report[4], the Pace Report states that the additional projected 28,000 fatal cancers due to Chernobyl releases would rise to about 140,000 in number. This value appears to be excessively high. As background, both the DOE Chernobyl Report[2] and the Anspaugh, et al. paper[3] were based on health effects models published in 1985 by the U.S. Nuclear Regulatory Commission (NRC) in the report NUREG/CR-4214[5] (hereafter referred to as the 1985 NUREG Report, of which Revision 1 was published in 1989 in anticipation of BEIR V revisions. An Addendum to Revision 1, Part II[6], hereafter cited as the 1991 NUREG Addendum, was issued by the NRC in 1991 to take into account the BEIR V changes, recommendations in Publication 60[7] of the International Commission of

Radiological Protection that was issued in 1991 (that also took into account the recommendations in BEIR V), and other recent reports on relevant health effects models.

Updated dose distribution projections were presented by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) in its 1988 report[8], with values of 22.6 and 80 million man-rems in the USSR and the Northern Hemisphere, respectively, from Chernobyl releases. Using the revised risk models from the 1991 NUREG Addendum and these updated dose distribution projections issued by UNSCEAR, revised additional fatal cancer projections have been estimated here, as given in the Attachment and related Figure, and shown in the table below:

Source	Coll. Committed Dose Man-rems (E+06)		Est: Add'l Fatal Cancers from Chernobyl (E+03)*	
	USSR	N.Hemisphere	USSR	N.Hemisphere
DOE/ER-0332 (1987)2	58	120	14	28
Anspaugh, et al. (1988)3	33	93	6.5	17
UNSCEAR	23	80	-	-
Catlin (this report)	23	80	10	34

*All estimates range down to zero at low dose and dose rates.

For the USSR population, the best (or central) estimate value has risen from a projected 6,500 to 10,000 fatal cancers, an increase by a factor of 1.5. The possibility of zero health effects at the very low doses and dose rates received by this population cannot be excluded. The percent excess over natural/ spontaneous cancers for this population has increased from 0.02% to about 0.03%. Using the summed site methodology cited above, the calculated risk coefficient is 460 excess cancer fatalities per million man-rem.

For the USSR population, the lower estimate of excess mortality has increased from 2,000 to 3,300 fatal cancers, while the upper estimate has decreased from 17,000 to about 13,000 fatal cancers. The corresponding updated rations of excess over natural/spontaneous cancer are 0.01% and about 0.04%, respectively. These projections are based on the 1991 NUREG models similar to those used for the central estimate, and the calculations are given in the Attachment. Calculated values have been rounded off to avoid implications of undue precision. Again, the possibility of excess health effects ranges to zero at very low does and dose rates generally encountered by these exposed populations.

Using the 1991 NUREG Addendum models and the 1988 UNSCEAR Report[8] dose distribution projections, the revised best (or central) estimate of additional fatal cancers in the 2.9 billion persons in the Northern Hemisphere from Chernobyl releases is calculated in this report to range from zero to about 34,000, a factor of 4 lower than the 140,000 additional cancer deaths attributed in the PACE Report to use of the 1990 BEIR V Report models. The percent excess over natural/spontaneous cancers for the population of the Northern Hemisphere is now estimated at 0.007%. Using the summed site methodology cited above, the calculated risk coefficient is 430 excess cancer fatalities per million man-rem.

The projected estimate of 185,000 non-fatal cancers discussed on page 381 of the PACE Report was made by Hohmeyer[9]. The physical juxtaposition of his citation between two DOE references gives the erroneous impression that this value originated in the DOE Chernobyl Report. Using the incidence risk models given in Table 3.22 of the 1991 NUREG Addendum together with the committed collective dose of 80 million man-rems from the 1988 UNSCEAR Report, a best estimate of the excess cancer morbidity in the 2.9 billion persons in the Northern Hemisphere has been made, on the order of about 80,000 cases, a factor of about 2.3 below that attributed to Hohmeyer in the Pace Report. For the population in the USSR, the estimated excess cancer morbidity due to Chernobyl is projected at 23,000 cases, roughly twice the projected excess morality. Again, the possibility of excess health effects ranges to zero at the very low doses and dose rates to which this population was exposed. The calculated incidence risk coefficient for the Northern Hemisphere and the USSR is about 1,000 additional cases per million man-rem.

In regard to the PACE Report statement on page 381 that Chernobyl would add 1,900 to the 180 million people DOE expects to be born with genetic disorders, projections of the normally expected and Chernobyl release-related cases have been calculated in this report, using the new risk models from Table 4.1 of the 1991 NUREG Addendum. For the 2.9 billion persons in the Northern Hemisphere, the normal incidence is estimated at 5.5 million cases, not the 180 million cited in the PACE Report. The central estimate risk factors for radiation-induced genetic disorders in the first generation for a dose of 1 rem to a total population of 1 million persons are 25 cases, taken from BEIR V, and 30 cases, using the 1991 NUREG Addendum table.

Using BEIR V risk coefficient of 25 cases per million man-rem, the number of additional genetic disorders from Chernobyl releases in the first generation in the Northern Hemisphere is estimated at 2,000, close to the number of 1,900 given in the Pace Report. Using the 30 cases per million man-rem given in the 1991 NUREG Addendum, this estimate would increase slightly to 2,400 additional cases in the first generation. The USSR component of these additional genetic disorders would be about 600 cases in the first generation, and the spontaneous generation due to natural causes would be about 16 million cases.

CONCLUSIONS

Considering that various publications cited above were issued in the 1988-1990 time period and available to the Pace investigators, it appears that the Pace Report lacks comprehensiveness and presents health risk estimates associated with Chernobyl releases that are too high. Hence, the Pace estimates do not support the derivations of environmental costs attributed to those health risks.

Reductions in the committed collective doses for the populations of the USSR territories and the Northern Hemisphere can be justified on the basis of newer studies now becoming available. For example, in its 1991 report on its Chernobyl Project[10], the International Atomic Energy Agency (IAEA) has noted that for nine city regions in the USSR, the doses to population groups determined by direct body measurements of radionuclide content from Chernobyl releases has been shown to be lower than those estimates given in earlier USSR official reports by factors of about 2 to 3. Several reasons have been hypothesized for these variances, including 1) conservatism or inaccuracies built into the environmental transport models used, 2) uncertainties associated with the use of various protective actions taken to reduce or block radionuclide intake, 3) inadequacy or inaccuracy in environmental conservative bias in scientific methodologies for assessment of doses and risks.

For these reasons, it is considered appropriate to reduce the committed collective dose assigned to the USSR from the 32.6 million man-rems used by Anspaugh, et al.[3] to the 22.6 million man-rem given in the 1988 UNSCEAR Report[8], and to modify the collective dose for the Northern Hemisphere accordingly. One should bear in mind that the regions reviewed by IAEA may not necessarily be typical of other regions in the USSR, possibly because they represent areas of highest radionuclide deposition where protective actions are likely to have been concentrated and effected.

The amount of reduction does not necessarily relate in a linear manner to the Northern Hemisphere where more sophisticated environmental transport modeling and measurement activities were conducted by numerous countries outside the USSR , and where, in many cases, protective actions to control radionuclide intakes were used sparingly or were not employed. For these reasons, the committed collective dose of 80 million man-rems given in the 1988 UNSCEAR Report has been retained without further change.

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PROJECTED CANCER MORTALITY (LIFETIME)
/UREG/CR–4214 RISK ESTIMATION MODELS – SUMMED SITES
CR42 LOW.WK1

ASSUMPTIONS	1985 MODEL	1991 MODEL
DOSE:	1 Gy = 1 Sv = 100 rem	1 Gy = 1 Sv = 100 rem
SEX:	50% female & 50% male (population)	53% female & 47% male (population)
AGE:	< 20 y, 16% female & 18% male	< 20 y, 16% female & 17% male
	≥ 20 y, 34% female & 32% male	≥ 20 y, 37% female & 30% male

POPULATION DOSE DISTRIBUTION – USSR		
AVG.INDIV.	COLL. COMM. DOSE (man–Gy)	
DOSE (Gy)	1985	1991
2.0	7,800	5,399
1.0	10,000	6,922
0.5	18,000	12,459
0.2	27,000	18,689
0.1	36,000	24,919
≤0.05	227,700	157,612
TOTAL	326,500	226,000

PROJECTED CANCER MORTALITY – USSR		
PRIMARY	LOWER BOUND MODELS	
CA SITE	1985	1991
Leukemia	271	638
Bone CA	11	59
Breast CA (F)	337	300
Lung CA	299	440
GI CA	514	887
Thyroid CA	229	158
Other CA	282	776
IN UTERO CA		
Leukemia	39	27
Other CA	39	27
TOTAL	**2,021**	**3,313**

NOTE:

For USSR population:
3,313 deaths/226,000 man–Gy =
1.5E–02 deaths/man–Gy (150 deaths/man–rem)

PRIMARY CA SITE	AVG.COMM. INDIV. DOSE (Gy)	AGE GROUP (y)	COLL.COMM. DOSE (man–Gy)	LIFETIME CA MORT. RISK/Gy	SPONT. DEATHS PER PERSON	RISK REDUCTION FACTOR	ESTIMATED LIFETIME EXCESS DEATHS
Leukemia	2.0		7,800	4.8E–03		1.00	37
	1.0		10,000	4.8E–03		0.70	34
	0.5		18,000	4.8E–03		0.40	35
	0.2		27,000	4.8E–03		0.22	29
	0.1		36,000	4.8E–03		0.16	28
	≤0.05		227,700	4.8E–03		0.10	109
Bone CA	2.0		7,800	2.0E–04		1.00	2
	1.0		10,000	2.0E–04		0.70	1
	0.5		18,000	2.0E–04		0.40	1
	0.2		27,000	2.0E–04		0.22	1
	0.1		36,000	2.0E–04		0.16	1
	≤0.05		227,700	2.0E–04		0.10	5
Breast CA (F)	2.0		3,900	45%	2.650E–02	1.00	47
	1.0		5,000	45%	2.650E–02	0.70	42
	0.5		9,000	45%	2.650E–02	0.40	43
	0.2		13,500	45%	2.650E–02	0.22	35
	0.1		18,000	45%	2.650E–02	0.16	34
	≤0.05		113,850	45%	2.650E–02	0.10	136
ung CA	2.0		7,800	5.3E–03		1.00	41
	1.0		10,000	5.3E–03		0.70	37
	0.5		18,000	5.3E–03		0.40	38
	0.2		27,000	5.3E–03		0.22	31
	0.1		36,000	5.3E–03		0.16	31
	≤0.05		227,700	5.3E–03		0.10	121
Gastro–	2.0		7,800	9.1E–03		1.00	71
intestinal CA	1.0		10,000	9.1E–03		0.70	64
	0.5		18,000	9.1E–03		0.40	66
	0.2		27,000	9.1E–03		0.22	54
	0.1		36,000	9.1E–03		0.16	52
	≤0.05		227,700	9.1E–03		0.10	207
Thyroid CA	External		326,500	7.0E–04		1.00	229
	Internal			7.0E–04		0.10	0
Other CA	2.0		7,800	5.0E–03		1.00	39
	1.0		10,000	5.0E–03		0.70	35
	0.5		18,000	5.0E–03		0.40	36
	0.2		27,000	5.0E–03		0.22	30
	0.1		36,000	5.0E–03		0.16	29
	≤0.05		227,700	5.0E–03		0.10	114
IN UTERO CA							
Leukemia	–		326,500	3.0E–04		0.40	39
Other CA	–		326,500	3.0E–04		0.40	39
						TOTAL	2,021

CR42LOW.WK1

NUREG/CR–4214 (1991) MODEL – LOWER ESTIMATE

PRIMARY CA SITE	AVG.COMM. INDIV. DOSE (Gy)	AGE GROUP (y)	COLL.COMM. DOSE (man–Gy)	LIFETIME CA MORT. RISK/Gy	SPONT. DEATHS PER PERSON	RISK REDUCTION FACTOR	ESTIMATED LIFETIME EXCESS DEATHS
Leukemia	2.0		5,399	9.7E–03		1.00	52
	1.0		6,922	9.7E–03		1.00	67
	0.5		12,459	9.7E–03		0.25	30
	0.2		18,689	9.7E–03		0.25	45
	0.1		24,919	9.7E–03		0.25	60
	≤0.05		157,612	9.7E–03		0.25	382
Bone CA	2.0		5,399	9.0E–04		1.00	5
	1.0		6,922	9.0E–04		1.00	6
	0.5		12,459	9.0E–04		0.25	3
	0.2		18,689	9.0E–04		0.25	4
	0.1		24,919	9.0E–04		0.25	6
	≤0.05		157,612	9.0E–04		0.25	35
Breast CA (F)	2.0		2,862	8.6E–03		1.00	25
	1.0		3,669	8.6E–03		1.00	32
	0.5		6,603	8.6E–03		0.25	14
	0.2		9,905	8.6E–03		0.25	21
	0.1		13,207	8.6E–03		0.25	28
	≤0.05		83,534	8.6E–03		0.25	180
ung CA	2.0		5,399	6.7E–03		1.00	36
	1.0		6,922	6.7E–03		1.00	46
	0.5		12,459	6.7E–03		0.25	21
	0.2		18,689	6.7E–03		0.25	31
	0.1		24,919	6.7E–03		0.25	42
	≤0.05		157,612	6.7E–03		0.25	264
Gastro–	2.0		5,399	1.4E–02		1.00	73
Intestinal CA	1.0		6,922	1.4E–02		1.00	93
	0.5		12,459	1.4E–02		0.25	42
	0.2		18,689	1.4E–02		0.25	63
	0.1		24,919	1.4E–02		0.25	84
	≤0.05		157,612	1.4E–02		0.25	532
Thyroid CA	External		226,000	7.0E–04		1.00	158
	Internal			7.0E–04		0.10	0
Other CA	2.0		5,399	1.2E–02		1.00	64
	1.0		6,922	1.2E–02		1.00	82
	0.5		12,459	1.2E–02		0.25	37
	0.2		18,689	1.2E–02		0.25	55
	0.1		24,919	1.2E–02		0.25	74
	≤0.05		157,612	1.2E–02		0.25	465
IN UTERO CA							
Leukemia	–		226,000	3.0E–04		0.40	27
Other CA	–		226,000	3.0E–04		0.40	27
						TOTAL	**3,313**

CR42LOW.WK1

PROJECTED CANCER MORTALITY (LIFETIME) Rev. 1 FEB 92
NUREG/CR–4214 RISK ESTIMATION MODELS – SUMMED SITES Page 1
CR42CEN.WK1

ASSUMPTIONS	1985	1991
DOSE:	1 Gy = 1 Sv = 100 rem	1 Gy = 1 Sv = 100 rem
SEX:	50% female & 50% male (population)	53% female & 47% male (population)
AGE:	< 20 y, 16% female & 18% male	< 20 y, 16% female & 17% male
	≥ 20 y, 34% female & 32% male	≥ 20 y, 37% female & 30% male

POPULATION DOSE DISTRIBUTION – USSR		
AVG.INDIV.	COLL. COMM. DOSE (man–Gy)	
DOSE (Gy)	1985	1991
2.0	7,800	5,399
1.0	10,000	6,922
0.5	18,000	12,459
0.2	27,000	18,689
0.1	36,000	24,919
≤0.05	227,700	157,612
TOTAL	326,500	226,000

PROJECTED CANCER MORTALITY – USSR		
PRIMARY	CENTRAL ESTIMATE MODELS	
CA SITE	1985	1991
Leukemia	560	1,156
Bone CA	23	107
Breast CA (F)	1,947	647
Lung CA	391	1,727
GI CA	2,205	3,677
Thyroid CA	229	158
Other CA	583	2,872
IN UTERO CA		
Leukemia	39	27
Other CA	39	27
TOTAL	**6,016**	**10,398**

NOTE:

For USSR population:
10,396 deaths/226,000 man–Gy =
4.6E–02 deaths/man–Gy (460 deaths/man–rem)

For the Northern Hemisphere population:
9,667 deaths/226,000 man–Gy x 800,000 man–Gy =
34,219 deaths

34,219 deaths/800,000 man–Gy =
4.3E–02 deaths/man–Gy (430 deaths/man–rem)

NUREG/CR–4214 (1985) MODEL – CENTRAL ESTIMATE

PRIMARY CA SITE	AVG.COMM. INDIV. DOSE (Gy)	AGE GROUP (y)	COLL.COMM. DOSE (man–Gy)	LIFETIME CA MORT. RISK/Gy	SPONT. DEATHS PER PERSON	RISK REDUCTION FACTOR	ESTIMATED LIFETIME EXCESS DEATHS
Leukemia	2.0		7,800	4.8E–03		1.00	37
	1.0		10,000	4.8E–03		0.77	37
	0.5		18,000	4.8E–03		0.54	47
	0.2		27,000	4.8E–03		0.39	51
	0.1		36,000	4.8E–03		0.35	60
	≤0.05		227,700	4.8E–03		0.30	328
Bone CA	2.0		7,800	2.0E–04		1.00	2
	1.0		10,000	2.0E–04		0.77	2
	0.5		18,000	2.0E–04		0.54	2
	0.2		27,000	2.0E–04		0.39	2
	0.1		36,000	2.0E–04		0.35	3
	≤0.05		227,700	2.0E–04		0.30	14
Breast CA (F)	–		163,250	45%	2.650E–02	1.00	1,947
Lung CA	2.0		3,900	18%	3.727E–02	1.00	26
	1.0		5,000	18%	3.727E–02	0.77	26
	0.5		9,000	18%	3.727E–02	0.54	33
	0.2		13,500	18%	3.727E–02	0.39	35
	0.1		18,000	18%	3.727E–02	0.35	42
	≤0.05		113,850	18%	3.727E–02	0.30	229
Gastro–	2.0		7,800	39%	4.846E–02	1.00	147
intestinal CA	1.0		10,000	39%	4.846E–02	0.77	146
	0.5		18,000	39%	4.846E–02	0.54	184
	0.2		27,000	39%	4.846E–02	0.39	199
	0.1		36,000	39%	4.846E–02	0.35	238
	≤0.05		227,700	39%	4.846E–02	0.30	1,291
Thyroid CA	External		326,500	7.0E–04		1.00	229
	Internal		–	7.0E–04		0.33	0
Other CA	2.0		7,800	5.0E–03		1.00	39
	1.0		10,000	5.0E–03		0.77	39
	0.5		18,000	5.0E–03		0.54	49
	0.2		27,000	5.0E–03		0.39	53
	0.1		36,000	5.0E–03		0.35	63
	≤0.05		227,700	5.0E–03		0.30	342
IN UTERO CA							
Leukemia	–		326,500	3.0E–04		0.40	39
Other CA	–		326,500	3.0E–04		0.40	39
						TOTAL	**6,016**

CR42CEN.WK1

NUREG/CR–4214 (1991) MODEL – CENTRAL ESTIMATE

PRIMARY CA SITE	AVG.COMM. INDIV. DOSE (Gy)	AGE GROUP (y)	COLL.COMM. DOSE (man–Gy)	LIFETIME CA MORT. RISK/Gy	SPONT. DEATHS PER PERSON	RISK REDUCTION FACTOR	ESTIMATED LIFETIME EXCESS DEATHS
Leukemia	2.0		5,399	9.7E–03		1.00	52
	1.0		6,922	9.7E–03		1.00	67
	0.5		12,459	9.7E–03		0.50	60
	0.2		18,689	9.7E–03		0.50	91
	0.1		24,919	9.7E–03		0.50	121
	≤0.05		157,612	9.7E–03		0.50	764
Bone CA	2.0		5,399	9.0E–04		1.00	5
	1.0		6,922	9.0E–04		1.00	6
	0.5		12,459	9.0E–04		0.50	6
	0.2		18,689	9.0E–04		0.50	8
	0.1		24,919	9.0E–04		0.50	11
	≤0.05		157,612	9.0E–04		0.50	71
Breast CA (F)	–		119,780	5.4E–03		1.00	647
Lung CA	2.0	≥ 20	5,399	30%	3.727E–02	1.00	60
	1.0	≥ 20	6,922	30%	3.727E–02	1.00	77
	0.5	< 20	4,112	60%	3.727E–02	0.50	46
	0.5	≥ 20	8,348	30%	3.727E–02	0.50	47
	≤ 0.2	< 20	66,402	60%	3.727E–02	0.50	742
	≤ 0.2	≥ 20	134,817	30%	3.727E–02	0.50	754
Gastro–intestinal CA	2.0	≥ 20	5,399	40%	4.846E–02	1.00	105
	1.0	≥ 20	6,922	40%	4.846E–02	1.00	134
	0.5	< 20	4,112	120%	4.846E–02	0.50	120
	0.5	≥ 20	8,348	40%	4.846E–02	0.50	81
	≤ 0.2	< 20	66,402	120%	4.846E–02	0.50	1,931
	≤ 0.2	≥ 20	134,817	40%	4.846E–02	0.50	1,307
Thyroid CA	External		226,000	7.0E–04		1.00	158
	Internal			7.0E–04		0.33	0
Other CA	2.0	≥ 20	5,399	25%	4.806E–02	1.00	65
	1.0	≥ 20	6,922	25%	4.806E–02	1.00	83
	0.5	< 20	4,112	110%	4.806E–02	0.50	109
	0.5	≥ 20	8,348	25%	4.806E–02	0.50	50
	≤ 0.2	< 20	66,402	110%	4.806E–02	0.50	1,755
	≤ 0.2	≥ 20	134,817	25%	4.806E–02	0.50	810
IN UTERO CA							
Leukemia	–		226,000	3.0E–04		0.40	27
Other CA	–		226,000	3.0E–04		0.40	27
						TOTAL	**10,398**

CR42CEN.WK1

NUREG/CR–4214 (1991) MODEL – CENTRAL ESTIMATE

NORTHERN HEMISPHERE

PRIMARY CA SITE	AVG.COMM. INDIV. DOSE (Gy)	AGE GROUP (y)	COLL.COMM. DOSE (man–Gy)	LIFETIME CA MORT. RISK/Gy	SPONT. DEATHS PER PERSON	N. HEMIS. RISK REDUC. FACTORS	REV.EST. LIFE RISK EX.DEATHS
Leukemia	2.0		5,399	9.7E–03		0.50	26
	1.0		6,922	9.7E–03		0.50	34
	0.5		12,459	9.7E–03		0.50	60
	0.2		18,689	9.7E–03		0.50	91
	0.1		24,919	9.7E–03		0.50	121
	≤0.05		157,612	9.7E–03		0.50	764
Bone CA	2.0		5,399	9.0E–04		0.50	2
	1.0		6,922	9.0E–04		0.50	3
	0.5		12,459	9.0E–04		0.50	6
	0.2		18,689	9.0E–04		0.50	8
	0.1		24,919	9.0E–04		0.50	11
	≤0.05		157,612	9.0E–04		0.50	71
Breast CA (F)	–		119,780	5.4E–03		0.50	323
Lung CA	2.0	≥ 20	5,399	30%	3.727E–02	0.50	30
	1.0	≥ 20	6,922	30%	3.727E–02	0.50	39
	0.5	< 20	4,112	60%	3.727E–02	0.50	46
	0.5	≥ 20	8,348	30%	3.727E–02	0.50	47
	≤ 0.2	< 20	66,402	60%	3.727E–02	0.50	742
	≤ 0.2	≥ 20	134,817	30%	3.727E–02	0.50	754
Gastro–Intestinal CA	2.0	≥ 20	5,399	40%	4.846E–02	0.50	52
	1.0	≥ 20	6,922	40%	4.846E–02	0.50	67
	0.5	< 20	4,112	120%	4.846E–02	0.50	120
	0.5	≥ 20	8,348	40%	4.846E–02	0.50	81
	≤ 0.2	< 20	66,402	120%	4.846E–02	0.50	1,931
	≤ 0.2	≥ 20	134,817	40%	4.846E–02	0.50	1,307
Thyroid CA	External		226,000	7.0E–04		0.50	79
	Internal			7.0E–04		0.33	0
Other CA	2.0	≥ 20	5,399	25%	4.806E–02	0.50	32
	1.0	≥ 20	6,922	25%	4.806E–02	0.50	42
	0.5	< 20	4,112	110%	4.806E–02	0.50	109
	0.5	≥ 20	8,348	25%	4.806E–02	0.50	50
	≤ 0.2	< 20	66,402	110%	4.806E–02	0.50	1,755
	≤ 0.2	≥ 20	134,817	25%	4.806E–02	0.50	810
IN UTERO CA							
Leukemia	–		226,000	3.0E–04		0.40	27
Other CA	–		226,000	3.0E–04		0.40	27
						TOTAL	9,667

CR42CEN.WK1

PROJECTED CANCER MORTALITY (LIFETIME)
NUREG/CR-4214 RISK ESTIMATION MODELS – SUMMED SITES
CR42UPP.WK1

ASSUMPTIONS	1985	1991
DOSE:	1 Gy = 1 Sv = 100 rem	1 Gy = 1 Sv = 100 rem
SEX:	50% female & 50% male (population)	53% female & 47% male (population)
AGE:	< 20 y, 16% female & 18% male	< 20 y, 16% female & 17% male
	≥ 20 y, 34% female & 32% male	≥ 20 y, 37% female & 30% male

POPULATION DOSE DISTRIBUTION – USSR		
AVG.INDIV.	COLL. COMM. DOSE (man-Gy)	
DOSE (Gy)	1985	1991
2.0	7,800	5,399
1.0	10,000	6,922
0.5	18,000	12,459
0.2	27,000	18,689
0.1	36,000	24,919
≤0.05	227,700	157,612
TOTAL	326,500	226,000

PROJECTED CANCER MORTALITY – USSR		
PRIMARY	UPPER BOUND MODELS	
CA SITE	1985	1991
Leukemia	1,567	2,192
Bone CA	69	203
Breast CA (F)	2,641	922
Lung CA	4,502	3,345
GI CA	6,171	3,448
Thyroid CA	229	158
Other CA	1,633	3,008
IN UTERO CA		
Leukemia	98	68
Other CA	98	68
TOTAL	17,007	13,413

NOTE:

For USSR population:
13,413 deaths/226,000 man-Gy =
5.9E-02 deaths/man-Gy (590 deaths/man-rem)

NUREG/CR–4214 (1985) MODEL – UPPER ESTIMATE

PRIMARY CA SITE	AVG.COMM. INDIV. DOSE (Gy)	AGE GROUP (y)	COLL.COMM. DOSE (man–Gy)	LIFETIME CA MORT. RISK/Gy	SPONT. DEATHS PER 10,000 POP.	RISK REDUCTION FACTOR	ESTIMATED LIFETIME EXCESS DEATHS
Leukemia	–		326,500	4.8E–03		1.00	1,567
Bone CA	–		326,500	2.1E–04		1.00	69
Breast CA (F)	–	<20	104,480	103%	1.048E–02	1.00	1,128
(female population)	–	≥20	222,020	42%	1.623E–02	1.00	1,513
Lung CA	–		326,500	37%	3.727E–02	1.00	4,502
Gastro–intestinal CA	–		326,500	39%	4.846E–02	1.00	6,171
Thyroid CA	External		326,500	7.0E–04		1.00	229
	Internal			7.0E–04		1.00	0
Other CA	–		326,500	5.0E–03		1.00	1,633
IN UTERO CA							
Leukemia	–		326,500	3.0E–04		1.00	98
Other CA	–		326,500	3.0E–04		1.00	98
						TOTAL	17,007

NUREG/CR–4214 (1991) MODEL – UPPER ESTIMATE

PRIMARY CA SITE	AVG.COMM. INDIV. DOSE (Gy)	AGE GROUP (y)	COLL.COMM. DOSE (man–Gy)	LIFETIME CA MORT. RISK/Gy	SPONT. DEATHS PER 10,000 POP.	RISK REDUCTION FACTOR	ESTIMATED LIFETIME EXCESS DEATHS
Leukemia	–		226,000	9.7E–03		1.00	2,192
Bone CA	–		226,000	9.0E–04		1.00	203
Breast CA (F)	–	<20	36,160	100%	1.048E–02	1.00	379
(female population)	–	≥20	83,620	40%	1.623E–02	1.00	543
Lung CA	–	<20	74,580	150%	1.448E–02	1.00	1,620
	–	≥20	151,420	50%	2.279E–02	1.00	1,725
Gastro–intestinal CA	–	<20	74,580	120%	1.774E–02	1.00	1,588
	–	≥20	151,420	40%	3.072E–02	1.00	1,860
Thyroid CA	External		226,000	7.0E–04		1.00	158
	Internal		–	7.0E–04		1.00	0
Other CA	–	<20	151,420	60%	1.830E–02	1.00	1,663
	–	≥20	226,000	20%	2.976E–02	1.00	1,345
IN UTERO CA							
Leukemia	–		226,000	3.0E–04		1.00	68
Other CA	–		226,000	3.0E–04		1.00	68
						TOTAL	13,413

PROJECTED CANCER INCIDENCE (LIFETIME)
NUREG/CR–4214 RISK ESTIMATION MODELS – SUMMED SITES
CR42INC.WK1

ASSUMPTIONS	1985	1991
DOSE:	1 Gy = 1 Sv = 100 rem	1 Gy = 1 Sv = 100 rem
SEX:	50% female & 50% male (population)	53% female & 47% male (population)
AGE:	< 20 y, 16% female & 18% male	< 20 y, 16% female & 17% male
	≥ 20 y, 34% female & 32% male	≥ 20 y, 37% female & 30% male

POPULATION DOSE DISTRIBUTION – USSR		
AVG.INDIV.	COLL. COMM. DOSE (man–Gy)	
DOSE (Gy)	1985	1991
2.0	7,800	5,399
1.0	10,000	6,922
0.5	18,000	12,459
0.2	27,000	18,689
0.1	36,000	24,919
≤0.05	227,700	157,612
TOTAL	326,500	226,000

PROJECTED CANCER INCIDENCE – USSR		
PRIMARY	CENTRAL ESTIMATE MODELS	
CA SITE	1985	1991
Leukemia	560	1,156
Bone CA	23	107
Breast CA (F)	1,947	1,905
Lung CA	391	1,727
GI CA	2,205	3,677
Thyroid CA	2,351	1,627
Other CA	2,182	2,872
Skin CA	875	10,034
TOTAL	**10,534**	**23,104**

NOTE:

For the USSR population:
The computation of 10,534 cancer cases has been made for comparison using the 1985 NUREG models and a collective dose of 326,500 man–Gy.

For the Northern Hemisphere population:
22,777 cases/226,000 man–Gy x 800,000 man–Gy = 80,617 cases

NUREG/CR–4214 (1985) MODEL – CENTRAL ESTIMATE – EXCESS INCIDENCE

PRIMARY CA SITE	AVG.COMM. INDIV. DOSE (Gy)	COLL.COMM DOSE (man–Gy)	LIFETIME CA INCID. RISK/Gy	SPONT. CASES PER PERSON	RISK REDUCTION FACTORS	ESTIMATED LIFETIME EXCESS CASES
Leukemia	2.0	7,800	4.8E–03		1.00	37
	1.0	10,000	4.8E–03		0.77	37
	0.5	18,000	4.8E–03		0.54	47
	0.2	27,000	4.8E–03		0.39	51
	0.1	36,000	4.8E–03		0.35	60
	≤0.05	227,700	4.8E–03		0.30	328
Bone CA	2.0	7,800	2.0E–04		1.00	2
	1.0	10,000	2.0E–04		0.77	2
	0.5	18,000	2.0E–04		0.54	2
	0.2	27,000	2.0E–04		0.39	2
	0.1	36,000	2.0E–04		0.35	3
	≤0.05	227,700	2.0E–04		0.30	14
Breast CA (F)	–	163,250	45%	2.650E–02	1.00	1,947
Lung CA	2.0	3,900	18%	3.727E–02	1.00	26
	1.0	5,000	18%	3.727E–02	0.77	26
	0.5	9,000	18%	3.727E–02	0.54	33
	0.2	13,500	18%	3.727E–02	0.39	35
	0.1	18,000	18%	3.727E–02	0.35	42
	≤0.05	113,850	18%	3.727E–02	0.30	229
Gastro–intestinal CA	2.0	7,800	39%	4.846E–02	1.00	147
	1.0	10,000	39%	4.846E–02	0.77	146
	0.5	18,000	39%	4.846E–02	0.54	184
	0.2	27,000	39%	4.846E–02	0.39	199
	0.1	36,000	39%	4.846E–02	0.35	238
	≤0.05	227,700	39%	4.846E–02	0.30	1,291
Thyroid CA	External	326,500	7.2E–03		1.00	2,351
	Internal	–	7.2E–03		0.33	0
Other CA	2.0	7,800	1.9E–02		1.00	146
	1.0	10,000	1.9E–02		0.77	144
	0.5	18,000	1.9E–02		0.54	182
	0.2	27,000	1.9E–02		0.39	197
	0.1	36,000	1.9E–02		0.35	236
	≤0.05	227,700	1.9E–02		0.30	1,277
Skin CA	–	326,500	6.7E–03		0.40	875
					TOTAL	**10,534**

CR42INC.WK1

NUREG/CR–4214 (1991) MODEL – CENTRAL ESTIMATE – EXCESS INCIDENCE

PRIMARY CA SITE	AVG.COMM. INDIV. DOSE (Gy)	AGE GROUP (y)	COLL.COMM DOSE (man–Gy)	LIFETIME CA INCID. RISK/Gy	SPONT. CASES PER PERSON	RISK REDUCTION FACTORS	ESTIMATED LIFETIME EXCESS CASES
Leukemia	2.0		5,399	9.7E–03		1.00	52
	1.0		6,922	9.7E–03		1.00	67
	0.5		12,459	9.7E–03		0.50	60
	0.2		18,689	9.7E–03		0.50	91
	0.1		24,919	9.7E–03		0.50	121
	≤0.05		157,612	9.7E–03		0.50	764
Bone CA	2.0		5,399	9.0E–04		1.00	5
	1.0		6,922	9.0E–04		1.00	6
	0.5		12,459	9.0E–04		0.50	6
	0.2		18,689	9.0E–04		0.50	8
	0.1		24,919	9.0E–04		0.50	11
	≤0.05		157,612	9.0E–04		0.50	71
Breast CA (F)	–		119,780	1.6E–02		1.00	1,905
Lung CA	2.0	≥ 20	5,399	30%	3.727E–02	1.00	60
	1.0	≥ 20	6,922	30%	3.727E–02	1.00	77
	0.5	< 20	4,112	60%	3.727E–02	0.50	46
	0.5	≥ 20	8,348	30%	3.727E–02	0.50	47
	≤ 0.2	< 20	66,402	60%	3.727E–02	0.50	742
	≤ 0.2	≥ 20	134,817	30%	3.727E–02	0.50	754
Gastro–intestinal CA	2.0	≥ 20	5,399	40%	4.846E–02	1.00	105
	1.0	≥ 20	6,922	40%	4.846E–02	1.00	134
	0.5	< 20	4,112	120%	4.846E–02	0.50	120
	0.5	≥ 20	8,348	40%	4.846E–02	0.50	81
	≤ 0.2	< 20	66,402	120%	4.846E–02	0.50	1,931
	≤ 0.2	≥ 20	134,817	40%	4.846E–02	0.50	1,307
Thyroid CA	External		226,000	7.2E–03		1.00	1,627
	Internal			7.2E–03		0.33	0
Other CA	2.0	≥ 20	5,399	25%	4.806E–02	1.00	65
	1.0	≥ 20	6,922	25%	4.806E–02	1.00	83
	0.5	< 20	4,112	110%	4.806E–02	0.50	109
	0.5	≥ 20	8,348	25%	4.806E–02	0.50	50
	≤ 0.2	< 20	66,402	110%	4.806E–02	0.50	1,755
	≤ 0.2	≥ 20	134,817	25%	4.806E–02	0.50	810
Skin CA	–		226,000	8.9E–02		0.50	10,034
						TOTAL	**23,104**

CR42INC.WK1

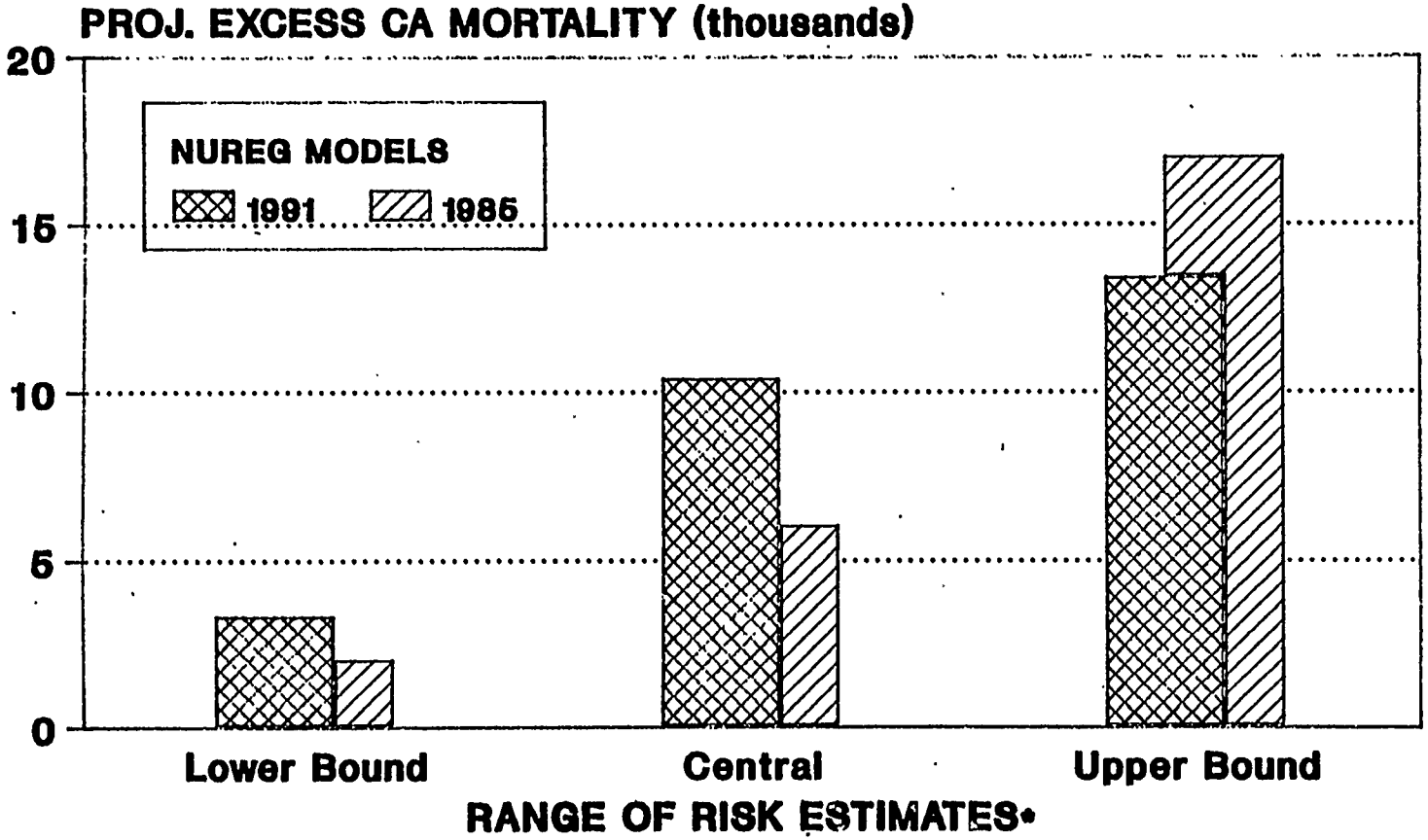
NUREG/CR–4214 (1991) MODEL – CENTRAL ESTIMATE – EXCESS INCIDENCE

NORTHERN HEMISPHERE

PRIMARY CA SITE	AVG.COMM. INDIV. DOSE (Gy)	AGE GROUP (y)	COLL.COMM DOSE (man–Gy)	LIFETIME CA INCID. RISK/Gy	SPONT. CASES PER PERSON	N.HEMIS RISK RED. FACTORS	REV.ESTIM. LIFETIME EXCESS CASES
Leukemia	2.0		5,399	9.7E–03		0.50	26
	1.0		6,922	9.7E–03		0.50	34
	0.5		12,459	9.7E–03		0.50	60
	0.2		18,689	9.7E–03		0.50	91
	0.1		24,919	9.7E–03		0.50	121
	≤0.05		157,612	9.7E–03		0.50	764
Bone CA	2.0		5,399	9.0E–04		0.50	2
	1.0		6,922	9.0E–04		0.50	3
	0.5		12,459	9.0E–04		0.50	6
	0.2		18,689	9.0E–04		0.50	8
	0.1		24,919	9.0E–04		0.50	11
	≤0.05		157,612	9.0E–04		0.50	71
Breast CA (F)	–		119,780	1.6E–02		1.00	1,905
Lung CA	2.0	≥ 20	5,399	30%	3.727E–02	0.50	30
	1.0	≥ 20	6,922	30%	3.727E–02	0.50	39
	0.5	< 20	4,112	60%	3.727E–02	0.50	46
	0.5	≥ 20	8,348	30%	3.727E–02	0.50	47
	≤ 0.2	< 20	66,402	60%	3.727E–02	0.50	742
	≤ 0.2	≥ 20	134,817	30%	3.727E–02	0.50	754
Gastro–intestinal CA	2.0	≥ 20	5,399	40%	4.846E–02	0.50	52
	1.0	≥ 20	6,922	40%	4.846E–02	0.50	67
	0.5	< 20	4,112	120%	4.846E–02	0.50	120
	0.5	≥ 20	8,348	40%	4.846E–02	0.50	81
	≤ 0.2	< 20	66,402	120%	4.846E–02	0.50	1,931
	≤ 0.2	≥ 20	134,817	40%	4.846E–02	0.50	1,307
Thyroid CA	External		226,000	7.2E–03		1.00	1,627
	Internal			7.2E–03		0.33	0
Other CA	2.0	≥ 20	5,399	25%	4.806E–02	0.50	32
	1.0	≥ 20	6,922	25%	4.806E–02	0.50	42
	0.5	< 20	4,112	110%	4.806E–02	0.50	109
	0.5	≥ 20	8,348	25%	4.806E–02	0.50	50
	≤ 0.2	< 20	66,402	110%	4.806E–02	0.50	1,755
	≤ 0.2	≥ 20	134,817	25%	4.806E–02	0.50	810
Skin CA	–		226,000	8.9E–02		0.50	10,034
						TOTAL	**22,777**

CR42INC.WK1

PROJECTED CANCER MORTALITY (LIFETIME)
USSR POPULATION FROM CHERNOBYL RELEASES
NUREG/CR-4214 Risk Estimation Models



•Possibility of zero health effects is not excluded at low doses & dose rates.

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Workshop Conclusions and Recommendations

Quantitative stochastic risk assessment is hindered by a lack of truly low level exposure data that accurately indicates the nature of the dose response curve. Furthermore, our inability to correctly account for the role of dose rate in stochastic risk assessment is particularly acute.

All current methods to address the problem are driven by the enormous data base from Japan, on the consequences of the atomic bombing in 1945. Although there are other epidemiology studies on exposed populations, none are as robust as that from Japan; thus any contrary indications are usually interpreted in terms of how they support rather than contradict the A-bomb data. With very few exceptions all the remaining studies are derived from the medical uses of radiation, where the exposures delivered by therapy and diagnostic machines were also absorbed at a relatively high rate.

All epidemiology studies also have the limitation of being unplanned studies wherein the dosimetry is determined retrospectively, thus carrying a level of uncertainty that may be too high for extensive extrapolation. Rarely do the studies cover more than one or two orders of magnitude. The very nature of all epidemiology studies is that the exposed study population is limited in size, is non-homogeneous, rarely perfectly matched to an untreated comparison control group, and in which the role of all confounding and co-factors in addition to dose cannot be completely known.

Independent studies of population residing in high natural background areas have not shown any stochastic radiation risk, but these are confined to small increments above "average". In the area of three to 3,000 times background there is little definitive information.

To add to the confusion, a plethora of radiation studies on mice, rats and dogs receiving defined chronic radiation studies have consistently demonstrated a very marked dose rate amelioration effect in stochastic end points. Inbred animals generally are sensitive to only one or a few radiogenic cancers, and thus no single clear universal factor has come from the laboratory. What this seems to obtain is the concept of a range of factors, not a single one; dose rate effectiveness factors which seem to increase in amelioration value as the dose rate is reduced.

The radiation research and protection community has consistently endorsed a linear no-threshold model in which the low dose and dose rate "slope" is 2-2.5 more shallow for small doses and low-dose rates.

The recent availability of a massive amount of data from the former Soviet Union provides information which appears to have the potential to fill in the "gap" in knowledge discussed above. Radiation exposures of over a half million people in the South Urals began with the development of the Soviet atomic

capability in the late '40s. For several years in the beginning, technological limitations contributed to large numbers of people receiving significant radiation exposures. These can be roughly considered as one of four sub-populations.

Starting in 1948, and mainly through about 1955, the population living near and along the Techa River were exposed to released radioactivity from the MAYAK atomic complexes; these exposures included ingestion of Sr-90, Cs-134,137 and other long-lived radionuclides. The environment-milk-child pathway was particularly significant.

Another population was exposed following a chemical explosion in a reprocessing facility in 1957, the Kyshtym accident. The atmospheric plume carried large concentrations of long-lived radionuclides for many tens of kilometers to the north, exposing the downwind population first to an inhalation exposure and then to an ingestion hazard for contaminated food and water.

In 1967, after a prolonged drought, a severe wind storm resuspended a new plume from a partially evaporated holding lake, (Karachay), and added new exposures to an area overlaying the trace a decade earlier.

Workers in the reactor complexes and in the chemical reprocessing facilities received significant radiation exposures, both internal and external, especially during the first decade.

As a part of the 1988-1993 Joint Coordinating Committee for Civilian Nuclear Reactor Safety, a "working group", (WG 7.2), was established to host a workshop and begin a review of the potential for the information from the South Urals to provide important answers to the question of low doses and dose rates. The tragic dimensions of the exposures are only now beginning to be fully understood. In June 1992, several experts were invited to an informal workshop to discuss the emerging data from Russia, to exchange some ideas on what had happened and what might be expected in the future and to suggest some initial activities. The format consisted of a series of informal paper presentations from the Russian experts and several summary seminars from the Americans to indicate the extent of and approaches to the published data.

Preliminary discussions of the Techa River-exposed populations included the fact that dose reconstruction had not been completed, although a significant amount of work had been done. Cohorts of inhabitants of villages at increasing distances from MAYAK provide a unique range of "dosage groups'. Several adjacent villages were evacuated at known times and provide information on shorter exposures. Some information on exposure geometry and diet is available, but has not been completely analyzed. Models of Sr-90 contamination had been developed; whole body counting of Bremmstrahlung, and of beta emissions from teeth and skull at earlier times, provide a record of actual individual doses.

Uncertainties about exposure and dose precision and accuracy were not completely evaluated.

Much of the data has been computerized. The originally exposed general population included a complete range of ages; most of the originally exposed younger people are still alive and many continue to be studied. It is possible to study at least three generations of exposed people; the children and grandchildren of those originally exposed around 1950. Some analysis of radioactivity of deceased persons is also available.

The principal exposure was from some external radiation emanating from the river and its banks plus that from ingestion of contaminated water and locally produced food. Although the exposures were protracted and continue into the present, the dose rates received were highest in the early years. It will be important to distinguish between dosage, i.e. intakes, and doses, exposures from previously deposited radioactivity. The pharmacokinetics of the radionuclides of concern vary with time, age, sex, ethnicity, and lifestyle. That many of those still alive continue to manifest body burdens provides an opportunity to directly validate many of the doses and models. Environmental dose reconstruction will be required to validate many of the dosimetric questions. Selective biological dosimetry will also aid in reducing dose uncertainty.

A spectrum of increased leukemias in the absence of increased bone cancers is attributed to Sr-90 ingestion by the Techa river populations. Peak bone marrow daily dose rates are estimated to range from about 0.1cGy to more than 0.1 Gy. Preliminary evaluation suggests that, relative to the information from the a-bomb survivors, the leukemia risk appears to be lower per unit of dose; perhaps a factor of two to four. It will be necessary to determine if the doses estimated neither under- or overestimate the dose situation.

Pathology and autopsy reports are available for many of the deceased. These have not been entered into an electronic data base as yet, although there are plans to do so. The preservation of all the data, some of which is in a most fragile state, is an essential early step in the work to be done.

The quarter million people living down wind from the 1957 and 1967 events are generally not those living along the Techa river. However the ethnic makeup of all the local populations is that of Russians, Tartars, and Baskirs. Each ethnic group has a unique lifestyle and diet, as well as different natural disease patterns. Because much of the dose is ingestion dependent, it is important to ascertain the principal dietary characteristics of the population over the past half century. There may be an excess in leukemias and solid cancers in this population.

About 12-15 thousand workers and their families live close to the MAYAK facilities. In the first half decade, starting in 1948, occupational exposures

exceeded current limits for most of the workers. The exposure patterns were different for those working at the production reactor facilities from those working in radiochemical processing facilities. External exposures exceeded one Gy annually for about a fourth of the radiochemical workers and about a tenth of the reactor workers. Significant inhalation doses were also recorded in the early days of technology development. Pulmonary doses of tens of Gy caused some fatalities from pulmonary impairment and later an increased risk for lung cancer. High doses are also estimated for skeleton and liver, particularly from plutonium and americium intakes. The families of non-workers manifest plutonium burdens which increase with age or residency time. Possible health effects in this population are not yet significant.

For persons heavily burdened with internal emitters, the continual exposure of sensitive tissues and organs has given rise to several hundred cases of chronic radiation sickness, (CRS), a disease which is different in many respects from acute radiation sickness. A complete evaluation of the characteristics of CRS, the compromising of essential physiology and its etiology is not yet available. Reduction in marrow stem cells and impairment of immunological function may be important aspects of the etiology. The stochastic risk implications for these individuals is not yet available.

Fundamental radiobiologic theories were discussed at the mathematical and molecular level. These tended to support a non-proportional relationship between doses delivered at low rates and subsequent risk. A preliminary model for radiation induced leukemia was presented and discussed which when related to peak dose rate, appeared to be best fitted by an exponential to the dose-rate effectiveness factor. The range of studies discussed, covered some 10 orders of magnitude in peak dose rates and suggest that at realistic multiples of natural background radiation, the effectiveness of the equivalent of lesion repair is so efficient as to reduce the leukemia risk by an order of magnitude or more, perhaps even defining a risk threshold.

Further work is needed to :

a) minimize the uncertainty regarding dosimetry and dose reconstruction, non-uniformity in time and space;

b) ascertain the completeness and accuracy of medical records, diagnosis, causes of death and role of possible competing factors;

c) specify doses in terms of total dose, average dose rate peak dose rate, mix of external and internal dose, and pharmacokinetics of internal distributions as relates to tissues at risk.

d) explore alternatives to quantifying risk beyond the traditional absolute and relative models.

e) use the information from laboratory studies on animals and cells as well as from improved biological dosimetric technology to better describe the absorbed doses and their consequences at widely varying dose rates.