Title

MATHEMATICAL MODELS AND EPIDEMIOLOGICAL SURVEYS: THEIR VALUE IN RISK ASSESSMENT OF THE HEALTH EFFECTS ON POPULATIONS OF EXPOSURE TO LOW LEVELS OF IONIZING RADIATION

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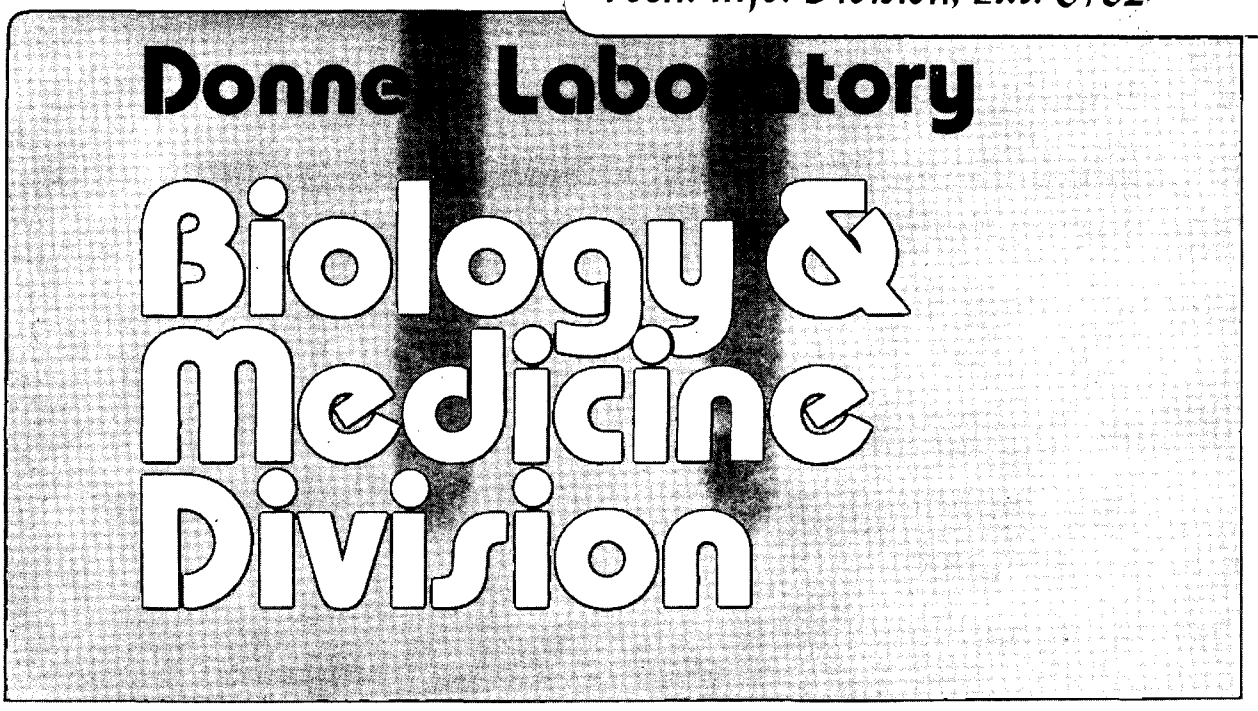

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DISCLAIMER

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Mathematical Models and Epidemiological Surveys: Their Value in Risk Assessment of the Health Effects on Populations of Exposure to Low Levels of Ionizing Radiation[1,2]

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Introduction

My assignment this evening is to try to provide you with some background to the current National Academy of Sciences' Report of the Committee on the Biological Effects of Ionizing Radiations, the BEIR-III Report (1), and in doing so, to help you understand why certain disagreements or controversies arose among the Committee members, and how they were or were not resolved. I think the best thing I can do is to set out to discuss the structure of the Report (1) and certain principles dealing with mathematical models and epidemiological surveys which were addressed in it. I will emphasize only one controversy, that leading to the problem of estimating numerical risk coefficients for radiation-induced cancer in human populations exposed to low-level radiation. Finally, I will briefly review certain of the important BEIR-III conclusions bearing on radiation-induced cancer in man, and cite only a limited number of risk estimtes derived from the available dose-response models and the epidemiological data. This is not to be construed as a summary of the BEIR-III Report (1)---I shall deal only with certain features of the Report (1), and in a manner which I view them.

The Charge to Advisory Comittees on Radiation

From the outset, the charge to the BEIR-III Committee and the composition of the membership of the Committee may have proven incompatible---hindsight tells us controversy was inevitable. It is important to realize that this was a so-called "balanced" committee of the National Academy of Sciences--a group of men and women selected for their expert knowledge and mature judgement, but also a scientific committee constituted so that different disciplines and thus different points of view would be brought to, voiced, and discussed in the committee forum (2). When different points of view fail to compel unified conclusions based not on the scientific facts and

experimental data, but rather on the interpretation, assessment and application of the facts and data, then disagreement and controversy are inevitable.

Take, for example, the charge to the BEIR-III Committee. The BEIR-III Committee had a good deal to do---to explain the terms of reference for preparation of the report, which was to bring the BEIR-III Report (3) up to date, to define its role, and to provide the report in a timely and appropriate fashion and written so that it might be understood by an informed public. But, the National Academy of Sciences was also given some very specific and knotty charges to deliberate. First, what was the state of radiobiological science to permit the use of laboratory animal data relevant to man for assessing the somatic hazards and genetic hazards to health of low-dose radiation in human populations? Second, based on theoretical radiobiology, microdosimetric theory, and radiobiological experimentation, what new knowledge was available for assessing dose-response relationships, both for high-LET and low-LET radiations, concerned with those health effects whose probability of occurrence, rather than severity, depended on dose---that is, somatic and genetic effects? Third, what new information was available on dose-rate effects covering high- and low-LET radiations and somatic and genetic effects, which could be applied to risk estimation in man? Fourth, what statistical models could be used from existing data to project into the future the potential risks to health of radiation exposure---both somatic and genetic health effects in human populations exposed at the present time? Specifically, how best to apply these risk projection models to radiation-induced cancer in man? Finally, to what extent can we identify additive or multiplicative effects among carcinogenic agents in man when one agent is ionizing radiation?

There were a number of additional charges, but these were the major ones to which the BEIR-III Committee was expected to respond after a respectable period of deliberation. In doing so, the problems were confounded by the request to bring to the Academy a report which would represent a consensus on the effects on populations of exposure to low levels of ionizing radiation relevant to current radiation protection philosophy. It included doses and dose rates of concern---what are the ranges of doses and dose rates in which various risk estimates for somatic and genetic harm are appropriate? It included practical considerations for human exposure---what are the differences in risks from acute and chronic exposure in man? It included numerical risk estimation based on the experimental data and epidemiological surveys---what are the numerical risk coefficients for somatic effects, that is, cancer-induction, and genetic effects, in humans exposed to low-dose radiation?

To carry out this broad charge the BEIR-III Committee, comprised of 24 scientists, provided a five-chapter report, with a few additional fringes (1). Chapter II concerned selected scientific principles employed in the analysis of radiation effects. Chapter III dealt with the sources and rates of natural and artificial man-made radiation exposure in the United States. Chapter IV was the report of the Subcommittee on Genetic Effects. Chapter V was the report of the Subcommittee on Somatic Effects dealing specifically with cancer-induction. Chapter IV was the report of certain members of the Subcommittee on Somatic Effects dealing specifically with those effects other than cancer. The Report is introduced with a comprehensive summary of the scientific considerations which led to the main conclusions of the BEIR-III Committee's deliberations.

Some Principles of Concern

Insofar as the Subcommittee on Genetic Effects is concerned, the scientists found, in large measure, that little new knowledge had become available since the 1972 BEIR-I Report (3) to alter the existing methods, approach, and assessment of genetic harm in human populations exposed to ionizing radiations. Thus, the paucity of human data compelled these scientists to depend primarily on laboratory animal data and dose-response models for deriving numerical risk coefficients for genetically-related ill-health in humans exposed to low-dose radiation. Some controversy arose concerning the role of germ cell population kinetics in the mouse, both in spermatagonial, and more importantly in oogonial cell renewal. But this did not deter the Subcommittee from reaching some consensus in its deliberations in spite of the fact that these important disagreements have yet to be satisfactorily resolved (4). In general, therefore, the sections dealing with genetic health effects do not suggest any substantive new knowledge to require significant revision of that so well documented in the BEIR-I Report (3). The conclusion to be drawn is that current radiation protection philosophy of dose limitation (5) adequately deals with the risks of genetic ill-health in exposed human populations at the present time.

It is in the matter of somatic risks, notably cancer-induction, that difficulties arose within the Subcommittee on Somatic Effects. Because there are no adequate or unifying theories or a full understanding of the fundamental mechanisms of carcinogenesis, the risks of cancer-induction due to radiation must be derived from biophysical theory, from mathematics, from experimental data, and from statistical methods in quantitative epidemiology. To understand why the Subcommittee chose to review in detail the scientific principles for numerical risk estimation for cancer-induction, three important areas should be considered. First is the relative biological effectiveness,

or RBE, particularly in the matter of neutron RBE, since this proves to be of importance in risk estimation at low doses. Second is the theoretical and radiobiological evidence relating dose to response. Third is the use of projection models, the absolute risk model and the relative risk model, which helps provide the framework for estimation of numerical risk coefficients utilizing statistical tools of quantitative epidemiology.

Relative biological effectivness may be defined as the ratio of the radiation dose of a high-LET radiation which produces the same biological effect as that due to a dose of a low-LET radiation. In general, the larger the amount of radiant energy deposited in a cell, the greater is the biological effect per unit dose, and the pattern of energy deposited depends strongly on the quality of radiation (6). Different LET radiations are known to cause different numbers of biological effects for the same absorbed dose. Therefore, the microdosimetric distribution of energy absorption in a defined localized volume within a vital structure, say DNA or perhaps the nucleus of the cell, becomes a very important factor. A microdosimetric quantity may be assigned to a theoretical linear-quadratic dose-response relationship which relates the microscopic distribution of energy or dose-absorption within a localized volume within the cell to LET (6). For low-LET radiation, this quantity is relatively small. At low doses, the quadratic term is unimportant. The linear term may be expected to be dominant at most doses for high-LET radiation. For high radiation doses, the quadratic term is dominant. This is seen in Figure 1. When the RBE is plotted against radiation dose levels where theory and experimental data are interdependent, then the range of dose required to demonstrate both linear and quadratic dependence is extremely large (1). The range of dose necessary to test the theory would cover perhaps three

orders of magnitude---a factor perhaps up to 1000. Few biological studies and no epidemiological surveys have covered this wide dose range necessary for proving correspondence between theoretical and experimental observations. Thus, enormous difficulties are to be expected in attempts to extrapolate over a very large dose range.

There are no experimental or epidemiological data linking dose and response at all levels or radiobiological investigation which permit a direct transition between radiobiological theory and valid experimental data and thereby the use of cells, tissues and animals to those situations appropriate for man. In addition, there is no single theory of carcinogenesis. Because the fundamental mechanisms of carcinogenesis remain elusive, it is not yet possible to define the shape of the dose-response curve in the low-dose region where human epidemiological data are lacking. Deriving any method of extrapolating from high-dose data without such information must take into account the wealth of mammalian cellular radiobiological research and our knowledge of cell injury, appropriate for both somatic and genetic injury at the level of the somatic cell, takes the general functional form:

$$I(D) = (\alpha_0 + \alpha_1 D + \alpha_2 D^2)\exp(-\beta_1 D - \beta_2 D^2)$$

where the incidence (I) at dose (D) is dependent on linear and quadratic functions of dose, and α_0, α_1, α_2, β_1, β_2 are positive (7-10). The exponential modifier represents a cell-killing function at high radiation doses. In actual practice, it is not possible to fit all the parameters. Depending on the dose term that dominates, the functional form can be modified, based in part on the values assigned to the coefficients, to simpler dose-response models---namely, the linear, where $I(D) = \alpha_0 + \alpha_1 D$, the quadratic, $I(D) = \alpha_0 + \alpha_2 D^2$, and the linear-quadratic, $I(D) = \alpha_0 + \alpha_1 D + \alpha_2 D^2$ dose-response relationships.

It is possible to obtain certain of the coefficients by fitting experimental data to the dose-response models. Indeed, all three models have been demonstrated to fit certain data in cell culture experiments, in animal studies, and in human epidemiological surveys. The characteristics of the three dose-response models include two main features: (1) There are initial upward-curving linear and quadratic functions of dose, which represent the process of radiation injury, such as cancer-induction by radiation; and (2) There is no threshold of dose below which the probability of injury does not occur. This latter observation is particularly important, since experimental proof of the existence of a threshold at very low doses proves, in practice, to be impossible.

Since there are no reliable human data documented for genetic effects in irradiated populations, the problem of assessing genetic risks in exposed human populations must depend almost entirely on studies of laboratory animals, particularly the mouse, and theoretical radiobiology. On the other hand, quantification of risks of somatic health effects, notably cancer-induction in exposed human populations, must depend largely on existing epidemiological surveys. Theoretical radiobiology and laboratory animal experiments cannot be used with the same reliability as in the case of genetic effects, and thus may only be used as supporting evidence (1,5,11). The problem of estimating risk coefficients appropriate for the low-dose region becomes extremely difficult, since in the absence of epidemiological data at low levels of exposure, the true dose-response relationships cannot be established from empirical data (7-10). Nevertheless, these relationships are essential in order to select a method appropriate to extrapolate from the epidemiological data on high-dose exposure to the low-dose region where no human data exist.

In order to chose a particular method for extrapolation, three major difficulties are encountered in any estimation of radiation risk coefficients based solely on human epidemiological surveys. First, there appears to be reasonably good agreement on cancer incidence among many cohort populations studied in exposed groups; however, the availability of reliably adequate control is not always feasible in each epidmiological survey (8). This makes it difficult to eliminate bias in statistical analysis. Second, there is great difficulty in assessing the validity or reliability of the precise radiation doses and dose rates in exposed humans---and this has become particularly evident in the present decision to re-evaluate the atomic bomb dosimetry in Hiroshima and Nagasaki (12). Finally, there is the problem of the long latent periods associated with cancer-induction between exposure to ionizing radiation and the appearance of cancer in the irradiated population. This latent interval can cover a span ranging from a few years to over four decades, and can even exceed the duration or period of follow-up.

Insofar as the cancer incidences and the radiation doses are concerned, every effort has been made to ascertain these with the greatest reliability, but problems arise, particularly in attempts to reconstruct the events of exposure many years previously. The matter of the long latent periods begs the important issue of how to project into the future the risk of cancer induced in individuals exposed at the present time---that is, the projection model appropriate to use for quantitating how the induced cancers will express themselves in time following exposure.

Two risk projection models, among many, are used by radiation epidemiologists; both are used in the BEIR-III Report (1)---the absolute risk model and the relative risk model. Figure 3 demonstrates how these characterize the expression of risk (1). The absolute risk is the expression of excess cancer risk due

to radiation exposure as the arithmetic difference between the risk among those exposed and that occurring in the absence of exposure (1). The absolute risk projection model takes into account the fact that the expression of radiation-induced cancers in the exposed population begins at some time after exposure (that is, after the minimal latent period) and continues at an excess rate for a further period, the period of expression. For leukemia, the period of expression may be taken as 25 years; for solid tumors, it is the duration of life (1). The absolute lifetime risk coefficient may be expressed as the total number of excess cancer cases in the exposed population per unit dose or per collective dose.

The relative risk is the expression of cancer risk due to exposure as the ratio of the risk among the exposed population to that occurring in the absence of exposure (1). The relative risk projection model expresses the excess of radiation-induced cancers as a ratio or multiple of the natural or spontaneous cancer rate, so that the excess risk is a multiple of the natural age-specific cancer rate in that study or cohort population. The greater the spontaneous rate of cancer incidence in a population, such as in an aging population, the greater will be the susceptibility of the individuals comprising that population to cancer-induction by radiation.

It must be remembered that no major epidemiological study of exposed human populations is as yet complete, and will not be until all members of the study population eventually die of natural or other causes. Only then can the complete cancer incidence in the irradiated and control populations be accurately ascertained. Thus, the distinction between the absolute and relative risk projection models becomes extremely important when the follow-up observation period is considered. When the observation periods are incomplete,

there can be at any one period of follow-up very wide differences in risk estimation. However, when the follow-up period is complete, and no more cancers occur in the study population, both the absolute and relative projection models should lead to the same numerical estimate for lifetime excess cancer risk, but the risk may be differently distributed in the exposed population. The two projection models give different results when projections are made beyond the period of follow-up or observation.

There is now sufficient epidemiological evidence available which indicates that, in general, most adult populations irradiated at older ages are at greater risk of cancer-induction. This age-dependence may be due to a higher induction rate or a shorter latent period, or both, but there are exceptions. For example, it is not known how this affects exposure of children.

The epidemiolgical evidence does not favor one projection model more than another; however, the age-dependence of cancer-induction by radiation favors the relative risk projection model somewhat more. The epidemiological data are insufficient to determine whether the excess cancr risk, once expressed in the exposed population, projects into the future, either as a relative risk or an absolute risk. The assumptions in the calculation of lifetime risk coefficients of radiation-induced cancer must take into account additional confounding factors, including sensitive genetic subgroups, and exposure to other potentially carcinogenic agents. These factors are important when considering differences between the absolute and relative projection models for estimation of risk.

Some Important Conclusions on Radiation Carcinogenesis in Man

There are many significant observations and conclusions summarized in the BEIR-III Report (1). Those dealing with somatic health effects may be focused into the following important points.

Cancer-induction is considered to be the most important somatic effect of low-dose ionizing radiation. Radiation-induced cancers in human populations occur with low frequency and are indistinguishable from cancers occurring spontaneously. Therefore, the excess induced in a population can only be detected on a statistical basis.

Radiation-induced cancer can occur in almost all human tissues. However, the rates of cancer-induction differ markedly depending on the tissue or organ. The natural or spontaneous rate of cancer incidence in the United States population varies significantly, over several orders of magnitude depending on a number of factors. The most important factors appear to be an age-dependence, a sex-dependence, and a site-dependence.

There is a greater susceptibility of certain tissues to cancer-induction by radiation. The major sites of radiation-induced cancers are the female breast, the thyroid, and the bone marrow, and to a lesser extent the lung, the digestive organs and bone. Because of the increased susceptibility of the breast and thyroid gland in females, the total radiation-induced cancer risk is necessarily greater in females than in males. Age is also a major factor in radiation-induced cancer risk. However, other factors, such as host factors, environmental factors, and immunological factors, also influence risk of cancer-induction by radiation.

Calculation of risk coefficients must take into account the long latent periods of solid tumor-induction and the extended period of expression. Dose-response relationships are still not known for most radiation-induced cancers, but the evidence suggests that the relationships depend on cancer site that is, the tissue or organ. For example, for breast cancer, the dose-incidence curves appear linear and independent of dose-rate (Figure 4) (14-16). For leukemia in the Nagasaki atomic bomb survivors, the epidemiological data fit a quadratic curve (Figure 5) (14).

Certain problems arise in estimation of dose and dose-rate from internal radiation exposure. When irradiation from radioactive internal emitters is involved, the effects are dependent in large measure on the distribution of dose in space and in time (17).

Cancer incidence, from a societal point of view, may be considered more important than cancer mortality. It is important to distinguish between the induction by radiation of normally nonfatal and curable tumors (e.g., thyroid or skin) and of normally fatal cancers (e.g., leukemia or lung). However, the data bases derived from autopsy information, death certificates, or tumor registries are not as reliable for cancer incidence as for cancer mortality.

Lastly, in the absence of epidemiological data in the low-dose region, at the present time, low-dose risk coefficients for radiation-induced cancer can only be obtained by extrapolating from observations at high doses using uncertain dose-response curves. During the preparation of the BEIR-III Report (1), a controversy arose among the members of the Subcommittee on Somatic Effects concerning the method of extrapolation to be used for estimating the numerical risk coefficients of cancer-induction from exposure to low-level radiation (9,10).

The BEIR-III Committee concluded two important observations: (1) It is not yet possible to make precise low-dose estimates for cancer induction by radiation because the level of risk is so low that it cannot be observed directly in man; and (2) There is great uncertainty as to the dose-response function most appropriate for extrapolating into the low-dose region (9,10). Faced with similar constraints, risk coefficients in the BEIR-I Report (3) some 10 years before were based on the linear dose-response model, and the true cancer risk coefficients could have been higher or lower than predicted.

Radiobiological theory and laboratory animal experiments now suggest a variety of dose-response relationships for cancer-induction, most having positive curvature for low-LET radiation at low doses, frequently with a small linear component and a larger quadratic component with increasing dose. It was this general dose-response curve---the linear-quadratic function with an exponential modifier in the cell-killing dose range---that emerged as the basis for the BEIR-III Committee's cancer risk analyses (Figure 2). Since the effect of cell killing was not indicated by any of the epidemiological data relevant to whole-body exposure to low-LET radiation, the data were fitted to a limited family of quadratic curves, from the linear, the linear-quadratic, and the pure quadratic dose-response models (1).

The Committee preferred linear-quadratic dose-response relationships, which are believed to be perhaps the best description for most, but not all, solid tumors induced by radiation. However, the Committee provided a range or envelope of risk estimates, derived from linear to pure quadratic dose-response relationships, calculating sex, age, and dose-specific risks for the three dose-response relationships, and for both the absolute and relative risk projection models.

In its final analyses, the majority of the members of the Committee preferred to emphasize that some experimental and human data, as well as theoretical considerations, suggest that for exposure to low-LET radiation, such as X-rays and gamma rays, at low doses, the linear model probably leads to overestimates of the risk of most radiation-induced cancers in man, but that the model can be used to define the upper limits of risk (Figure 4) (1,10). Similarly, a majority of the members of the Committee believed that the pure quadratic model may be used to define the lower limits of risk from low-dose,

low-LET radiation (1,10). The Committee generally agreed, for exposure to high-LET radiation, such as neutrons and alpha particles, linear risk estimates for low doses are less likely to overestimate the risk and may, in fact, underestimate the risk (1). Furthermore, the Committee, in its report, emphasized that the collective influence of the many uncertainties in estimation of the carcinogenic risk in man of low-level radiation was such as to deny great credibility to any estimates of human cancer risk that can be made for low-dose, low-LET radiation, and that emphasis should be placed on the approach to the method of risk coefficient estimation rather than any numerical values derived thereby (1).

Estimation of Risk Coefficients for Radiation-Induced Cancer

In the BEIR-III Report (1) the various illustrative radiation exposure conditions, the dose-response curves, and the risk projection models, based primarily on the Japanese atomic-bomb survivor data, provided a large number of tables of estimated risk coefficients for radiation-induced cancer in human populations exposed to low levels of low-LET radiation. It is worthwhile to illustrate one such example from the Report (1)---that of the estimated excess cancer deaths among one million population exposed to 10 rads (0.1 Gy) of low-LET whole-body radiation. Here, the linear-quadratic dose-response model predicts increases that range from 0.5% to 1.4% over the normal expectation of cancer mortality of approximately 164,000 per million persons depending on the projection model used (Table 1). For the linear model, the values are only about twice these, whereas the pure quadratic model predicts values about one-eighth those of the linear-quadratic dose-response relationship. Generally, for low-LET radiation, the BEIR-III Committee preferred the linear-quadratic dose-response model and concluded that it provided the most realistic risk estimates.

Comparison with the 1972 BEIR-I Report (3) risk estimates, and 1977 UNSCEAR Report (11) risk estimates, based on a cancer risk per average rem of exposure, indicates that all the values are very similar. This is important since the BEIR-I and UNSCEAR cancer risk estimates are based solely on the linear hypothesis.

Implications for Radiation Protection and Public Policy

Two main questions confronted the BEIR-III Committee from the outset (1). Both dealt indirectly with matters of radiation protection philosophy and the system of dose limiation (5) presently employed, and both had their genesis in the BEIR-I Committee's deliberations (3).

First, in the consideration of members of the public and public health policy, will radiation effects be expected to occur at dose levels occurring from annual exposure of a few hundred millirems (or a few millisieverts) in addition to natural background and medical exposure? At the present time, there is no clear answer, but the BEIR-III Committee concluded that in most cases, linear extrapolation from high-dose data leads to overestimation of risk from low-dose, low-LET radiation. The linear model is not likely to overestimate the effects of high-LET radiation, amd may, in fact, underestimate them when high-dose data are in the cell-killing dose region.

Second, for the radiation worker population in industry and medicine, will delayed or late health effects occur at levels of exposure in the range of 0.5 to 5 rems per year (or 5 to 50 mSv per year)? Here the BEIR-III Committee concluded delayed health effets could occur in those radiation workers with lifetime occupational exosures which may be accumulated by continuously working close to the recommended dose limits, i.e. to the maximum permissible dose (5).

These two important questions and their answers compel three important conclusions on risk perception, decision-making and public policy. First,

the BEIR-III Report (1) reflects the state of our scientific knowledge and its limitations. It is just not possible to provide a single numerical estimate to define radiation risk, and this is confounded in the low-dose region of practical concern where no human epidemiological evidence is available. Second, the BEIR-III Report (1) does not set radiation protection standards. Thus, the Report (1) does not seek sweeping simplifications of complex radiation protection problems, and it recognizes that current radiation protection philosophy of dose limiation does not necessarily depend on accurate or precise definition of risk (5). Finally, and perhaps most important, on the basis of the range of the radiation risk estimates derived, any lack of numerical precision does not minimize either the need for setting responsible public health policies, nor the conclusion that such risks are extremely small when compared with those available of alternative options, and those normally accepted by society as the hazards of everyday life.

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TABLE I

Cancer-Induction in One Million Persons Following
Single Exposure to 10 rads (0.1 Gy) of Low-LET Radiation (1)

Dose-Response Model			Absolute Risk Model	Relative Risk Model
	Normal expectation of cancer deaths		163,800	163,800
Linear-quadratic	Excess:	number	766	2255
		percentage	0.47	1.4
Linear	Excess:	number	1671	5014
		percentage	1.0	3.1
Quadratic	Excess:	number	95	276
		percentage	0.058	0.17

FIGURE LEGENDS

Fig. 1. Dose-effect relationship derived from radiobiological theory and experimental evidence (6). ζ is a microdosimetric quantity which is assigned to a theoretical linear-quadratic curve; it relates the microscopic distribution of energy within a localized volume within the cell to LET. The solid line is the sum of the linear (L) and quadratic (Q) contributions to the effect. The coordinates are logarithmic scales (1).

Fig. 2. Alternative dose-response models for radiation-induced cancer in exposed human populations (1). The functional form may be considered a complex functional quadratic equation; however, the linear function is perhaps the most important, and the α_0 and α_1 are the parameters relevant to risk at very low doses. This function may be modified that allows expression of upward curvature at low doses (α_2) and downward curvature at high doses (β_1 and β_2) to account for cell-killing effects. Depending on the values of the coefficients, the functional form reduces to simpler models---the linear (B), the pure quadratic (C), and the linear-quadratic (quadratic with a linear term in the low-dose region).

Fig. 3. Risk of cancer-induction following radiation. The constant absolute (solid line) and relative (dash line) risk models are plotted against age. A, age at time of irradiation (X); B, age at end of minimal latent period (LP); C, age at a given time after excess cancer risk is expressed.

Fig. 4. Dose-response curves of breast cancer incidence relative to estimated radiation dose to the breast (13). The epidemiological surveys include the Japanese atomic bomb survivors, postpartum mastitis patients, and tuberculosis patients in Massachusetts and Nova Scotia. All the data sets in these surveys fit a linear dose-response model, with no suggestion for a quadratic term.

Fig. 5. Leukemia incidence in Japanese atomic bomb survivors in Hiroshima and Nagasaki (14). The relative risk is plotted against the T65 kerma (dose). The Nagasaki data set fits a quadratic dose-response model, with no suggestion for a linear term. These curves may be expected to change when the re-estimation of dosimetry of the Japanese atomic bombs is completed in the future (12).

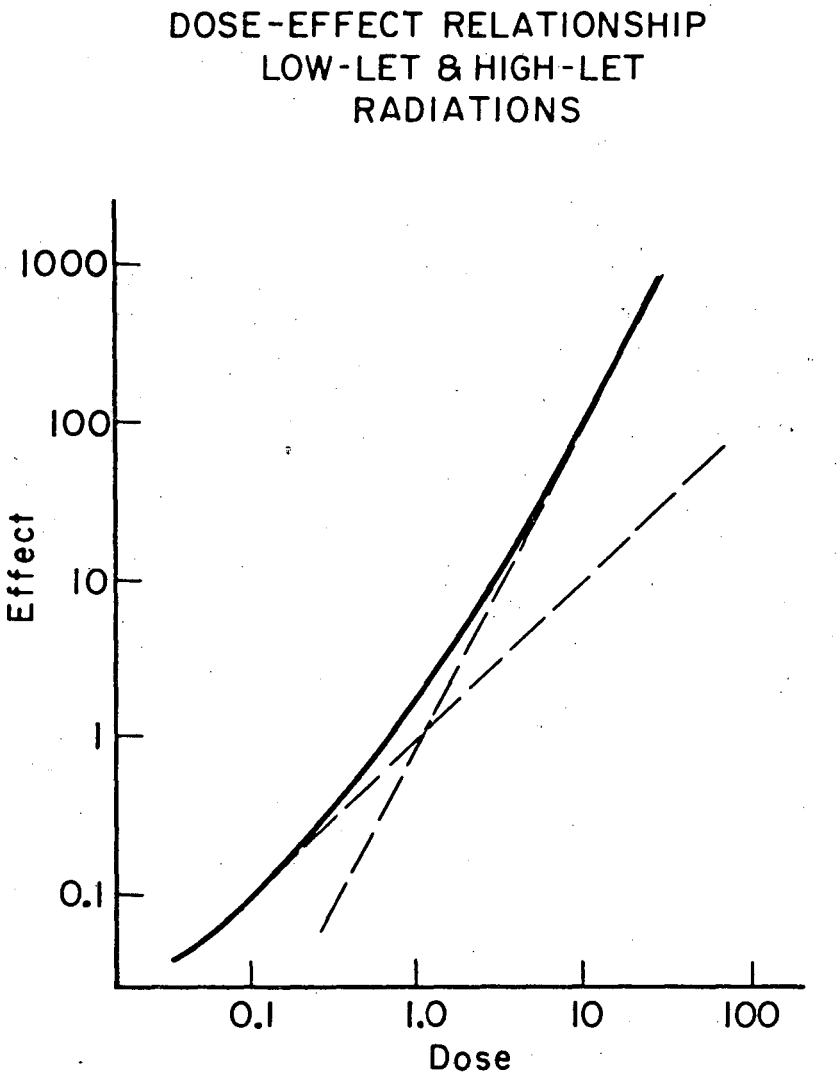

Figure 1

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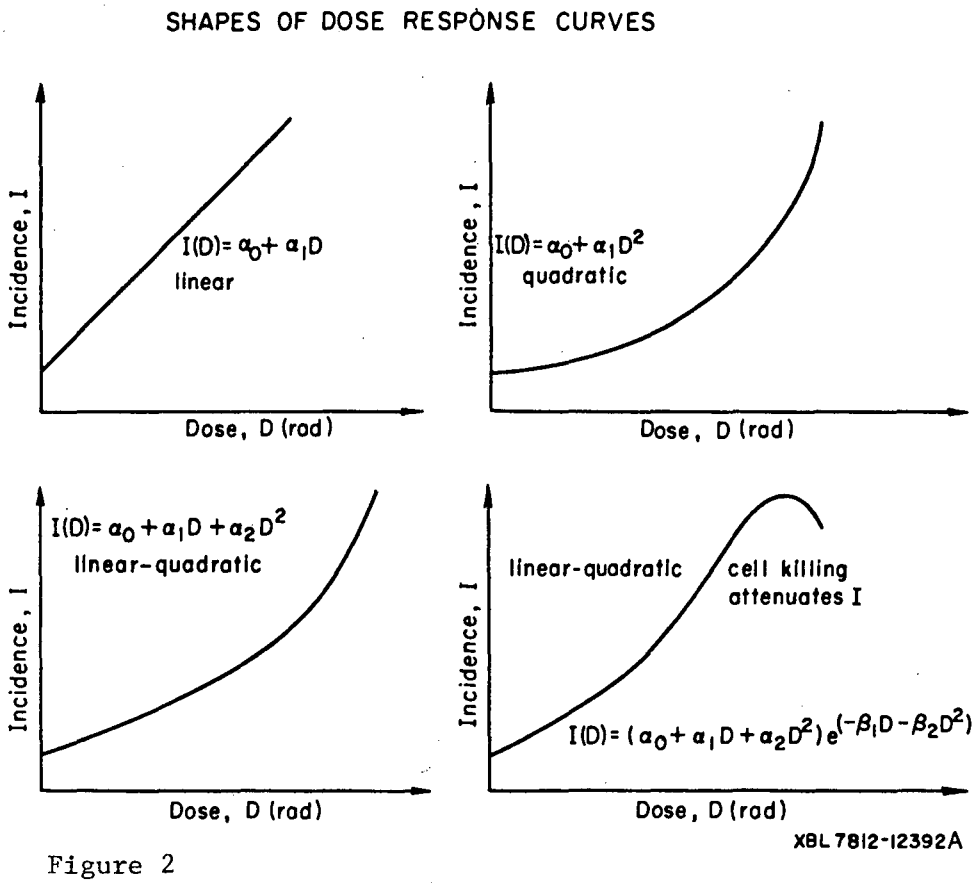
SHAPES OF DOSE RESPONSE CURVES
Incidence, I
I(D)= α0+ α1D
linear
Dose, D (rad)
Incidence, I
I(D)= α0+ α1D2
quadratic
Dose, D (rad)
Incidence, I
I(D)= α0 + α1D + α2D2
linear-quadratic
Dose, D (rad)
Incidence, I
linear-quadratic
cell killing
attenuates I
I(D)= (α0+ α1D + α2D2) e(-β1D - β2D2)
Dose, D (rad)
XBL 7812-12392A

Figure 2

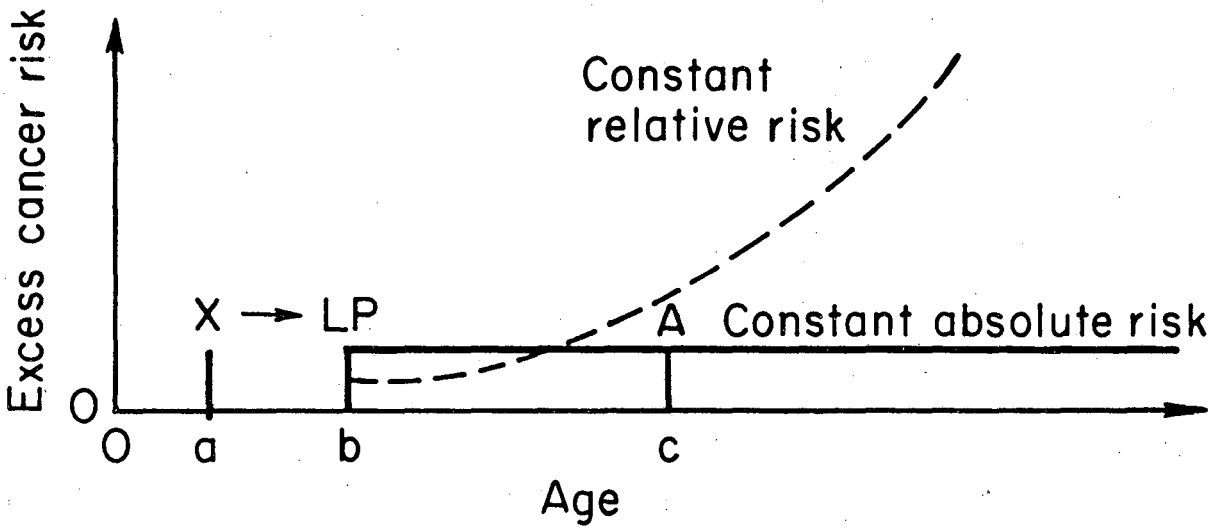

Figure 3

XBL801-3028

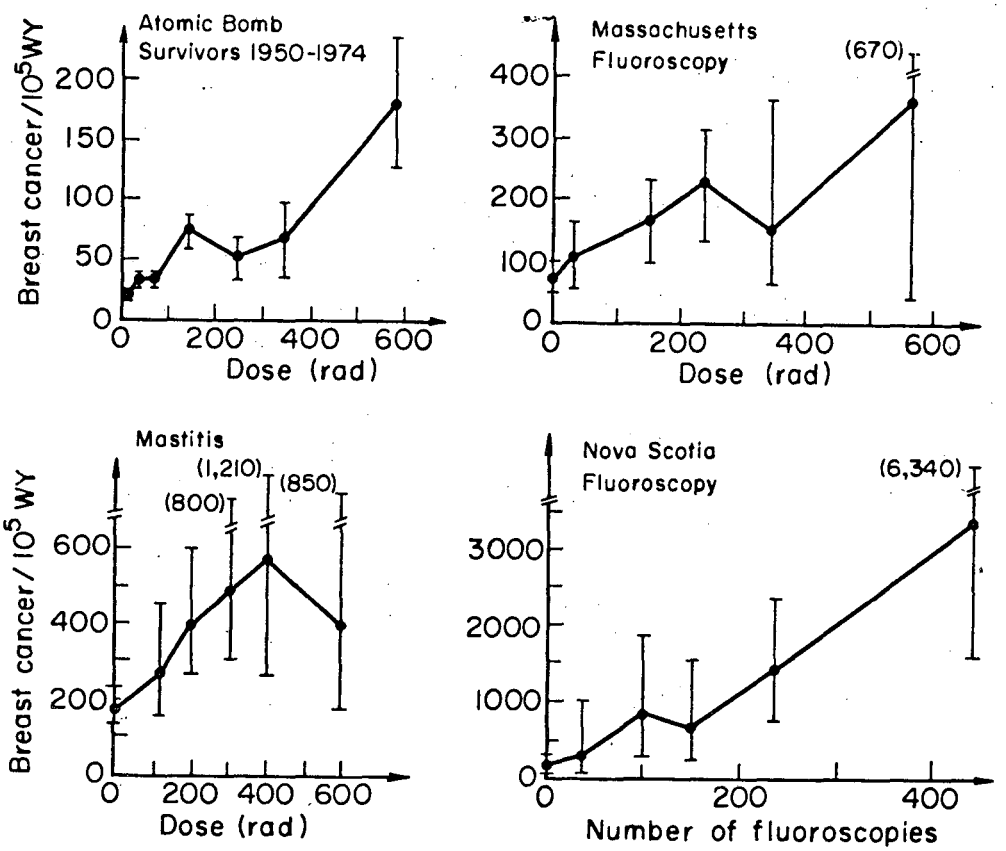

Figure 4

XBL815-3792

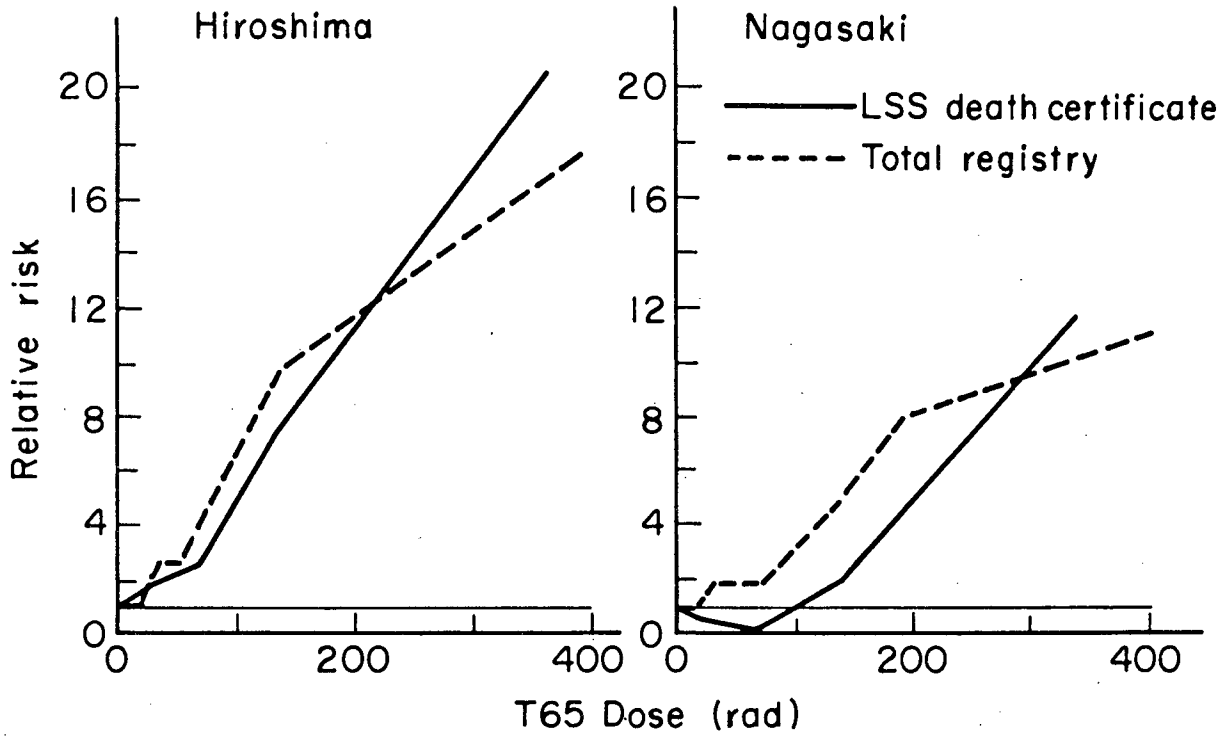

Figure 5

XBL815-3791

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