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The BEIR-III Report: Origin of the Controversy

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EDITOR'S NOTE

During the preparation of the National Academy of Sciences-National Research Council BEIR-III Report, a controversy arose among members of the Subcommittee on Somatic Effects concerning the method to be used for estimating the risk of cancer-induction from low-level radiation. Dr. Fabrikant was asked to serve as chairman of a consultative group to advise the Assembly of Life Sciences, NRC, on the BEIR-III Report to "restate in a balanced manner the diversity of views concerning the biological effects of low-dose low-LET ionizing radiation." Dr. Fabrikant reviews the work of the Committee, the background for the controversy, and the scientific basis for its resolution.

WHAT IS THE BEIR-III REPORT [1]?

The current Report [1] of the Committee on the Biological Effects of Ionizing Radiation (The BEIR-III Report) is the record of the deliberations of an expert scientific advisory committee of the National Academy of Sciences - National Research Council, and deals with the scientific basis of the health effects in human populations exposed to low levels of ionizing radiation. The Report [1] broadly encompasses two areas. (1) It reviews the current scientific knowledge—epidemiological surveys and laboratory animal experiments—relevant to radiation exposure of human populations and to the late health effects of low-level radiation. (2) It evaluates and analyzes these late health effects—both somatic and genetic effects—in relation to the risks to health from exposure to low-level radiation. The Committee presently consists of 22 members, selected for their expertise in areas of biology, biophysics, biostatistics, epidemiology, genetics, mathematics, medicine, physics, public health, and the radiological sciences. The reports [1-3] of the BEIR Committee have become reference texts for the scientific basis for development of radiation protection standards and for public health policy, and therefore profoundly influence decision-making for the regulation of societal activities involving ionizing radiations.

The 1972 BEIR-I Report [2] and the 1980 BEIR-III Report [1] differ from one or more of the other radiation advisory committee reports of the UNSCEAR [4], the ICRP [5], the NCRP [6], and of other national councils and committees, in four important ways. (1) The BEIR Report is intended to be a readable, usable document for those societal activities concerned with radiation and health. (2) The BEIR Committee does not set radiation standards or public health policy. However, the Committee's reports are purposefully presented so that they will be useful to those responsible for decision-making concerning regulatory programs and public health policy involving radiation in the United States.

(3) The epidemiological surveys and laboratory animal data are reviewed and assessed for their value in estimating numerical risk coefficients for the late health effects, and particularly cancer, in human populations exposed to low-level radiation. (4) The Report addresses the continued need to assess and evaluate the benefits from those activities involving radiation as well as the risks.

It was within this framework that the BEIR-III Committee pursued its responsibilities from the beginning of 1977 to January 1979. At that time there appeared to be a majority for support within the Subcommittee on Somatic Effects for the method to estimate the cancer risk for low-dose, low-LET whole-body radiation. With what would have been a dissenting position on the part of some, and the recognition of a need to move on quickly to complete the Report, the BEIR-III Report [1] was released on May 2nd, 1979. There would have been no reason to release the Report, in my opinion, if there had not been some assurance prior to that time that a reasonable, but not necessarily unanimous, consensus had been achieved within the Committee. However, it is since that time that the so-called BEIR-III "controversy" surfaced for public admonition. This "controversy" centered on the Committee's most difficut task—to estimate the carcinogenic risk of low-dose, low-LET whole-body radiation.

WHAT ARE THE UNCERTAINTIES IN THE DOSE-RESPONSE RELATIONSHIPS FOR RADIATION-INDUCED CANCER?

The BEIR-III Committee recognized three serious limitations constraining precise numerical estimation of excess cancer risk of low-level radiation in exposed human populations. First, we lack an understanding of the fundamental mechanisms of cancer-induction by radiation, particularly in man. Second, the

dose-response data from epidemiological surveys are highly uncertain, particularly at low levels of dose. Third, experimental and theoretical considerations suggest that various and different dose-response relationships may exist for different radiation-induced cancers in exposed human populations.

In recent years, a general hypothesis for estimation of excess cancer risk in irradiated human populations, based on theoretical considerations, on extensive laboratory animal studies, and on limited epidemiological surveys, suggests various and complex dose-response relationships between radiation dose and observed cancer incidence [7-9]. Among the most widely considered models for cancer-induction by radiation, based on the available information and consistent with both knowledge and theory, takes the complex quadratic form: $I(D) = (\alpha_0 + \alpha_1 D + \alpha_2 D^2)\exp(-\beta_1 D - \beta_2 D^2)$, where I is the cancer incidence in the irradiated population at radiation dose D in rad, and α_0, α_1, α_2, β_1 and β_2 are non-negative constants (Figure 1). This multicomponent dose-response curve contains (1) initial upward-curving linear and quadratic functions of dose, which represent the process of cancer-induction by radiation; and (2) a modifying exponential function of dose, which represents the competing effect of cell-killing at high doses. α_0 is the ordinate intercept at 0 dose, and defines the natural incidence of cancer in the population. α_1 is the initial slope of the curve at 0 dose, and defines the linear component in the low-dose range. α_2 is the curvature near 0 dose, and defines the upward-curving quadratic function of dose. β_1 and β_2 are the slopes of the downward-curving function in the high-dose range, and define the cell-killing function. Analysis of a number of dose-incidence curves for cancer-induction in irradiated populations, both in humans and in animals, has demonstrated that for different radiation-induced cancers only certain of the parameter values of these constants can be theoretically determined. Therefore, it has become necessary to simplify the model by reducing the number of parameters which

would have the least effect on the form of the dose-response relationship in the dose range of low-level radiation. Such simpler models, with increasing complexity, include the linear, the pure quadratic, the quadratic (quadratic function with a linear term in the low-dose region), and finally, the multi-component quadratic form with a linear term and with an exponential modifier (Figure 2).

WHAT IS THE BEIR-III CONTROVERSY ?

While there is no precise definition of low-level exposure, many scientists generally agree that low-level radiation is that which falls within the dose range considered permissible for occupational exposure. According to accepted standards [10], 5 rem per year to the whole body would be an allowable upper limit of low-level radiation dose for the individual radiation worker. In this context, it could be concluded that most of the estimated delayed cancer cases which may be associated with levels of diagnostic radiation exposure, or with a so-called hypothetical nuclear reactor accident, or even after prolonged periods of occupational exposure among radiation workers, are therefore considered by some scientists to be caused by exposures well below these allowable limits. Furthermore, if it is assumed that any extra radiation above natural background, however small, causes additional cancer, then if millions of people are exposed, as in the case of diagnostic radiology, some extra cancers will inevitably result. Other scientists strongly dispute this, and firmly believe that low-level radiation is nowhere near as dangerous as their adversarial colleagues would contend. Central to this dispute, it must be remembered that cancers induced by radiation are indistinguishable from those occurring naturally; hence, their existence can be inferred only on the basis of a statistical excess above the natural incidence. Since such health effects, if any, are so rarely seen under low-level radiation because the exposures are so small, the issue of this dispute may never be resolved—it may be beyond the abilities of science and mathematics to decipher.

It is this type of controversy that was at the root of the division within the present BEIR-III Committee. There is little doubt that the Committee's most difficult task was to estimate the carcinogenic risk of low-dose, low-LET whole-body radiation. Here, to the disquiet of some of the members of the Committee, emphasis was placed almost entirely on human epidemiological studies, since it was felt by the majority of the members that little information from laboratory animal and biophysical studies could be applied directly to man. Therefore, as the earier 1972 BEIR-I Report [2] had done, some members of the present BEIR-III Committee considered it necessary to adopt a linear hypothesis of dose-response to estimate the cancer risk at very low-level radiation exposure where no human epidemiological data are available. Here, it is assumed the same proportional risks are present at low levels as at high levels of radiation. This position implied that even very small doses of radiation are carcinogenic, a finding that, for example, could force the Environmental Protection Agency and the Food and Drug Administration to adopt stricter health standards to protect against occupational and general population exposure. Other members of the Committee did not accept this linear position. When there is no human epidemiological evidence at low doses of low-LET radiation, these scientists prefer to assume that the risks of causing cancer are proportionally lower.

On the basis of the experimental evidence and current microdosimetric theory, and on the limited epidemiological data, therefore, the present BEIR-III Committee could reasonably adopt as the basis for its consideration of dose-response models the quadratic from with a linear term in the low-dose region/. (linear-quadratic dose-response model) In the Committee's attempts to apply derivatives of the multicomponent, linear-quadratic dose-response model to the epidemiological data, simplification was necessary to obtain statistically stable risk estimates in many cases. Certain members of the BEIR-III Committee were passionately

divided on this matter; some members of the Committee strongly favor the linear model, others favor the pure quadratic form. A further modification of the linear-quadratic form was assumed with the linear and quadratic components to be equivalent at some dose, which is consistent with the epidemiological data and the radiobiological evidence, and avoids dependence on either of the two extreme forms.

Most of the members of the Committee recognized that, in large part, the available human data from epidemiological studies fail to suggest any specific dose-response model, and are not sufficient reliable to discriminate among a priori models suggested by the experimental and theoretical studies. However, there appears, at present, to be certain exceptions from the human experience. For example, cancer of the skin is not observed at low radiation doses, and dose-response relationships for the Nagasaki leukemia data appear to have positive curvature [11]. The incidence of breast cancer induced by radiation seems to be adequately described by a linear dose-response model (Figure 3) [9,12]. 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. 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. The Committee generally agreed, that 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.

WHAT ARE THE UNCERTAINTIES IN ESTIMATION OF THE CARCINOGENIC RISK IN MAN OF LOW-LEVEL RADIATION ?

The estimation of the carcinogenic risk of low-dose, low-LET radiation is subject to numerous uncertainties. The greatest of these concerns the shape of the dose-response curve. Others include the length of the latent period, the RBE for fast neutrons and alpha radiation relative to gamma and x-radiation, the period during which the radiation risk is expressed, the model used in projecting risk beyond the period of observation, the effect of dose rate or dose fractionation, and the influence of differences in the natural incidence of specific types of cancer. In addition, uncertainties are introduced by the biological risk characteristics of humans, for example, the effect of age at irradiation, the influence of any disease for which the radiation was given therapeutically, and the influence of length of observation or follow-up of the study populations. The collective influence of these uncertainties is such as to deny great credibility to any estimates of human cancer risk that can be made for low-dose, low-LET radiation.

WHAT ARE THE SOURCES OF EPIDEMIOLOGICAL DATA FOR THE ESTIMATION OF EXCESS CANCER RISK IN EXPOSED HUMAN POPULATIONS?

The tissues and organs about which we have the most reliable epidemiological data on radiation-induced cancer in man, obtained from a variety of sources from which corroborative risk coefficients have been estimated, include the bone marrow, the thyroid, the breast, and the lung. The data on bone and the digestive organs are, at best, preliminary, and do not approach the precision of the others. For several of these tissues and organs, risk estimates are obtained from very different epidemiological surveys, some followed for over 25 years, and with adequate control groups. There is good agreement when one considers the lack of precision inherent in the statistical analyses of the case-finding and cohort study populations, variability in ascertainment and

clinical periods of observation, age, sex and racial structure, and different radiation dose levels, and constraints on data from control groups.

The most reliable data have been those of the risk of leukemia, which come from the Japanese atomic bomb survivors [11], the ankylosing spondylitis patients treated with x-ray therapy in England and Wales [13], the metropathia patients treated with radiotherapy for benign uterine bleeding [14], the tinea capitis patients treated with radiation for ringworm of the scale [15], and the early radiologists [16]. There is evidence of an age-dependence and a dose-dependence, a relatively short latent period of a matter of a few years, and a relatively short period of expression, some 10 years. This cancer is uniformly fatal.

The data on thyroid cancer are more complex. These surveys include the large series of children treated with radiation to the neck and mediastinum for enlarged thymus [17], children treated to the scalp for tinea capitis [15], and the Japanese atomic bomb survivors [11] and Marshall Islanders [18] exposed to nuclear explosions. Here, there is an age-dependence and sex-dependence—children and females appear more sensitive. Although the induction rate is high, the latent period is relatively short, and it is probable that no increased risk will be found in future follow-up of these study populations. In addition, most tumors are either thyroid nodules, or benign or treatable tumors, and only a few are fatal.

Much information has become available on radiation-induced breast cancer in women [9,12]. The surveys include primarily women with tuberculosis who received frequent fluoroscopic examinations for artificial pneumothorax [19], postpartum mastitis patients treated with radiotherapy [20], and the Japanese atomic bomb survivors in Hiroshima and Nagasaki [11]. Here, there is an age-dependence and dose-dependence, as well as a sex-dependence; the latent period is long, some 20 to 30 years. Perhaps about half of these neoplasms are fatal.

Another relatively sensitive tissue, and a complex one as regards radiation dose involving parameters of the special physical and biological characteristics of the radiation quality, is the epithelial tissue of the bronchus and lung. These surveys include the Japanese atomic bomb survivors [11], the uranium miners in the United States and Canada [21], and the ankylosing spondylitis patients in England and Wales [13]. There is some evidence of age-dependence from the Japanese experience, and a relatively long latent period. This cancer is uniformly fatal.

The risk of radiation-induced bone sarcoma, based primarily on surveys of the radium and thorium patients who had received the radioactive substances for medical treatment, or ingested them in the course of their occupations [22], is low. For all other tumors arising in various organs and tissues of the body, values are extremely crude and estimates are, at best, preliminary.

WHAT ARE THE RISK ESTIMATES OF RADIATION-INDUCED CANCER IN MAN ?

After much deliberation and a good deal of difficult debate, the BEIR-III Committee chose three exposure situations for illustrative computations of the lifetime cancer risk of low-dose, low-LET whole-body radiation: (1) a single exposure of representative (life-table) population to 10 rads; (2) a continuous, lifetime exposure of a representative (life-table) population to 1 rad per year; and (3) an exposure to 1 rad per year over several age intervals exemplifying conditions of occupational exposure. These three exposure situations were not chosen to reflect any circumstances that would normally occur, but embrace the areas of concern—general population and occupational exposure and single and continuous exposure.

Much dissatisfaction and disagreement attended the choice of these particular dose levels to be used for illustrative purposes. Some members of the BEIR-III Committee strongly felt that below these three dose levels, which

were arbitrarily chosen for the current Report, the uncertainties of extrapolation to very low-dose levels were too great to justify any attempt at risk estimation. Other members felt just as strongly that risk estimates for cancer-induction by radiation could be reliably calculated at dose levels of 1 rad or even much less. These differences were never satisfactorily settled. The selected annual level of chronic exposure of 1 rad per year, although only one-fifth the maximal permissible dose for occupational exposure, is nevertheless consistent with the occupational exposure experience in radiology and in the nuclear industry.

In the absence of any increased radiation exposure, among one million persons of life-table age and sex composition in the United States, about 164,000 persons would be expected to die from cancer, according to present cancer mortality rates. For a situation in which these one million persons are exposed to a single dose increment of 10 rads of low-LET radiation, the linear-quadratic model predicts increases of about 0.5 percent and 1.4 percent over the normal expectation of cancer mortality, according to the projection model used. For continuous lifetime exposure to 1 rad per year, the increase in cancer mortality, according to the linear-quadratic model, ranges from about 3 percent to 8 percent over the normal expectation, depending on the projection model. The upper and lower limits of these cancer mortality risk estimates suggest a very wide range or envelope of values which may differ by as much as an order of magnitude, or more. The uncertainty derives mainly from the dose-response models used, from the alternative absolute and relative projection models, and from the sampling variation in the source data. The lowest risk estimates—the lower bound of the envelope—are obtained from the pure quadratic model; the highest—the upper bound of the envelope—from the linear model; and the linear-quadratic model provides estimates intermediate between these two extremes.

There was a good deal of reluctance by some Committee members to introduce cancer-incidence data—for the first time in any report—for purposes of risk estimation. Since cancer mortality data are considered far more reliable than comparable incidence data, cancer incidence risk estimates are less firm than mortality estimates. However, the Committee also recognized that the incidence of radiation-induced cancer provides a more complete expression of the total social cost than dose mortality. For continuous lifetime exposure to 1 rad per year, for example, and based on the linear-quadratic model, the increased risks expressed as percent of the normal incidence of cancer in males were about 2 percent to 6 percent, depending on the projection model. Risks for females were substantially higher than those for males, due primarily to the relative importance of radiation-induced thyroid and breast cancer.

WHAT ARE THE IMPLICATIONS OF NUMERICAL RISK ESTIMATION FOR RADIOLOGY, RADIATION PROTECTION AND PUBLIC HEALTH POLICY?

The BEIR-III Committee did not highlight any controversy over the health effects of low-level radiation. In its evaluation of the epidemiological surveys and the laboratory animal data, the Committee carefully reviewed and assessed all the available scientific evidence for estimating numerical risk coefficients for the health effects in human populations exposed to low-level radiation. Such devices require scientific judgment and assumptions based on the available data only, and have necessarily and understandably led to some disagreement not only outside the Committee room, but among Committee members, as well. But such disputes and disagreements center not on the scientific facts and not on the existing epidemiological or experimental data, but rather on the assumptions, interpretations, and analyses of the available facts and data.

The present scientific evidence and the interpretation of available epidemiological data can now draw some reliable conclusions on which to base

radiation protection standards for public health policy. The setting of any permissible radiation level or guide, however, remains essentially an arbitrary procedure. Based on the radiation risk estimates derived, any lack of 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. Unless man wishes to dispense with those activities which inevitably involve exposure to low levels of ionizing radiations, he must recognize that some degree of risk to health, however small, exists. In the evaluation of such risks from radiation, it is necessary to limit the radiation exposure to a level at which the risk is acceptable both to the individual and to society. When compared with the benefits that society has established as goals derived from the necessary activities of medical care and of energy production, it is apparent that society must establish appropriate standards and seek appropriate controlling procedures which continue to assure that its needs and services are being met with the lowest possible risks.

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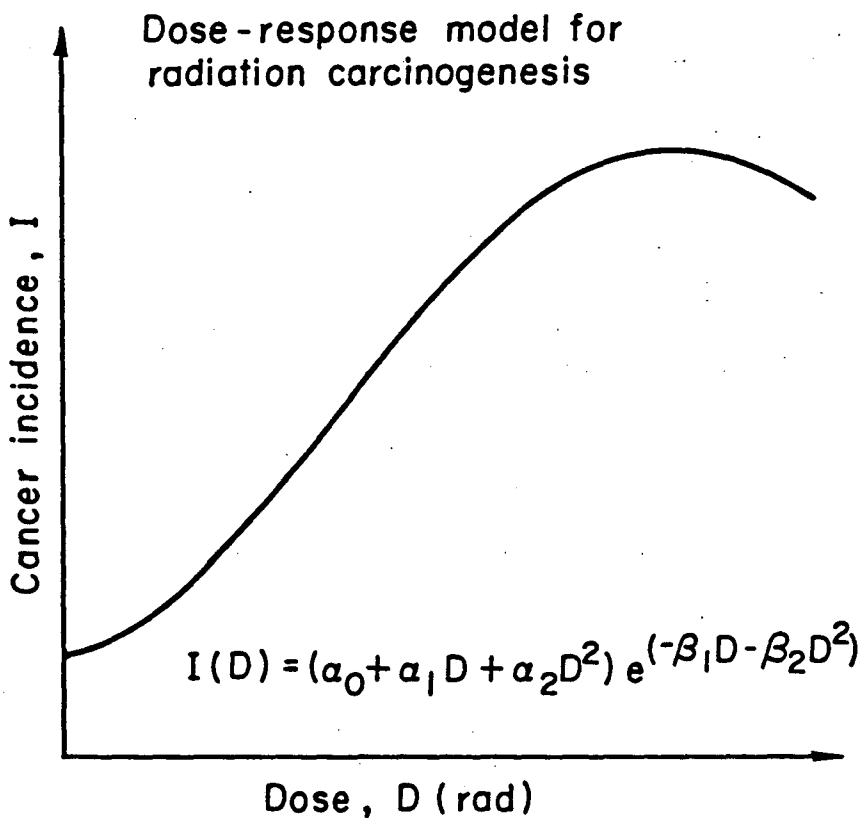

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Fig. 1

SHAPES OF DOSE RESPONSE CURVES

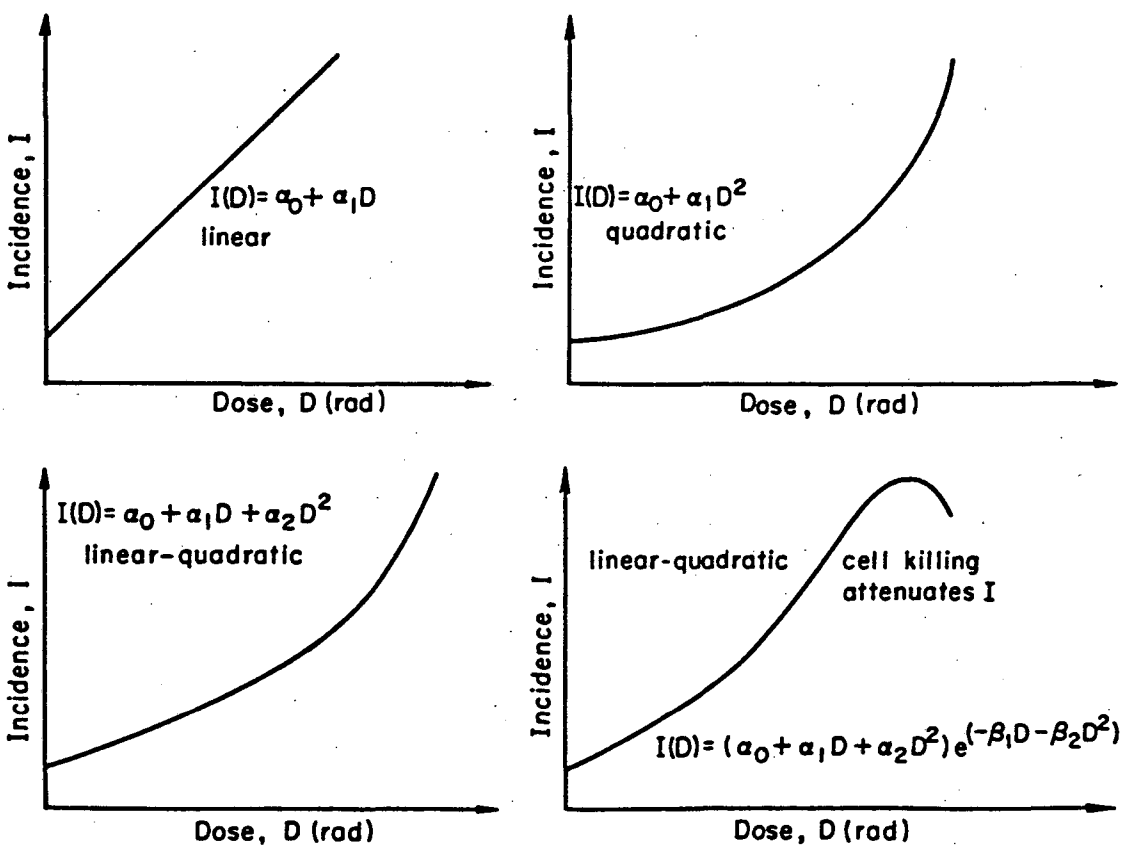

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Fig. 2

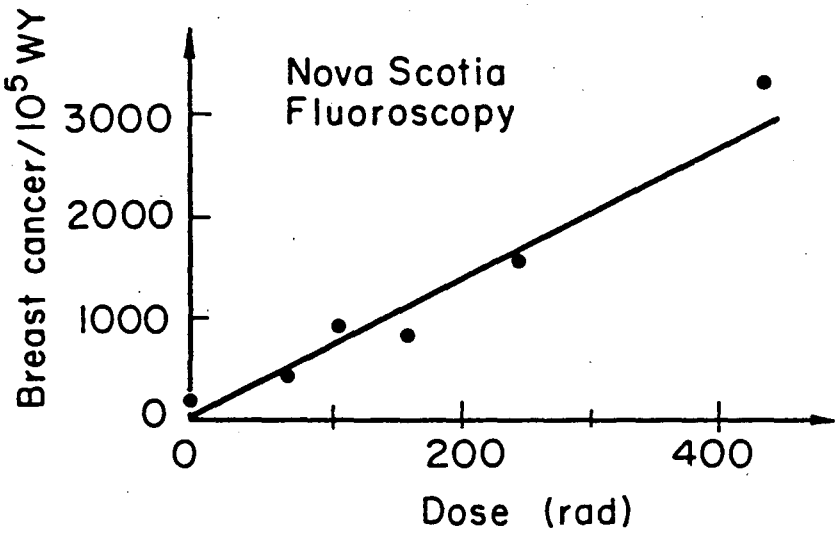

Fig. 4

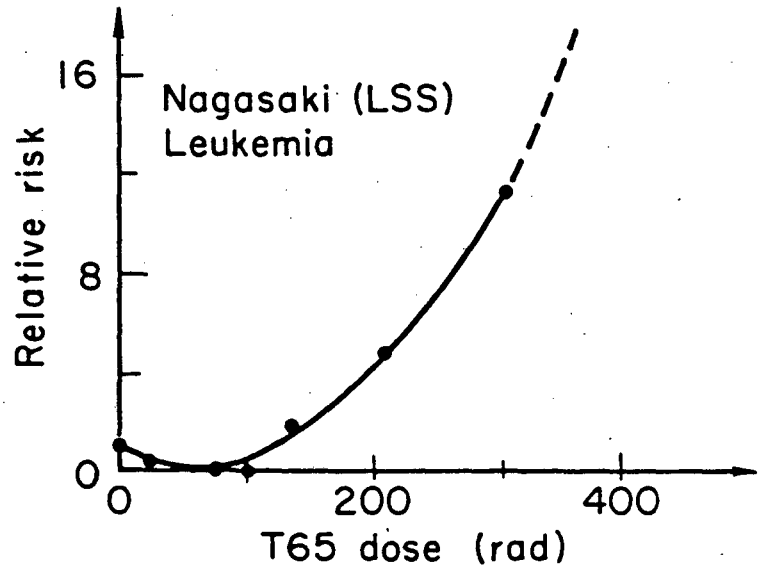

Fig. 3

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