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RADIATION CARCINOGENESIS IN MAN: INFLUENCE OF DOSE-RESPONSE MODELS AND RISK PROJECTION MODELS IN THE ESTIMATION OF RISK COEFFICIENTS FOLLOWING EXPOSURE TO LOW-LEVEL RADIATION

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RADIATION CARCINOGENESIS IN EXPOSED HUMAN POPULATIONS

The somatic effects of concern in human populations exposed to low doses and low dose rates of ionizing radiations are those that may be induced by muttion in individual cells, singly or in small numbers (1). The most important of these is considered to be cancer induction. Current knowledge of the carcinogenic effect of radiation in man has been reviewed to two recent reports: the 1977 Report of the United Nations Scientific Committee on the Effects of Atomic Radiation, the 1977 UNSCEAR Report (2), and the 1980 Report of the National Academy of Sciences Committee on the Biological Effects of Ionizing Radiations, the BEIR-III Report (1). The epidemiological data analyzed derive mainly from studies of the Japanese atomic bomb survivors in Hiroshima and Nagasaki, of patients in England and Wales treated with X-irradiation for ankylosing spondylitis, and of several other groups of people irradiated from external or internal sources, either for medical reasons or from occupational exposure. Both reports emphasize that cancers of the breast, thyroid, hematopoietic tissues, lung, and bone can be induced by radiation. Other cancers, including the stomach, pancreas, pharynx, lymphatic, and perhaps all tissues of the body, may also be induced by radiation. ¶ Both reports calculate risk estimates in absolute and relative terms for low-dose, low-LET whole-body exposure, and for leukemia, breast cancer, thyroid cancer, lung cancer, and other cancers. These estimates derive from exposure and cancer incidence data at high doses (frequently greater than 0.5 Sv) and at high dose rates (most frequently greater than 0.5 Sv per minute) (1-3). There are no compelling scientific reasons to apply these values of risk per cSv derived from high doses and high dose rates to the very low doses and low dose rates of concern in human radiation protection. In the absence of reliable human data for calculating risk estimates

at very low doses and low dose rates, neither the UNSCEAR nor BEIR Committees felt confident to predict the reliability of such extrapolation (1-4).

DOSE-RESPONSE MODELS: EXTRAPOLATION FROM ANIMAL DATA TO MAN. Benign and malignant tumors of almost any type or site may be induced by irradiation in animals. Susceptibility to radiation carcinogenesis varies widely among cells, tissues, organs, and organisms, depending on the influences of species differences, genetic composition, age, sex, physiological state, and other constitutional and environmental factors. Although all ionization radiations appear qualitatively similar in carcinogenic activity, they vary considerably in carcinogenic effectiveness per cSv, depending on the dose and on the distribtion of the radiation in time and space (1-6). ¶ The dose-incidence relationships for cancer induction in animals have not been characterized sufficiently over a wide range of radiation doses, dose rates, and LET to enable accurate risk estimation at doses below 50 cSv. Wide variations occur in the shapes of the dose-response curves for cancers for cancers of different types and for cancers of the same type in different animal species and in the same species. the incidence of tumors to be expected under determined exposure conditions cannot be predicted confidently by extrapolation from observations in animals or in man on other neoplasms or other exposure conditions (1-6). ¶ In spite of these uncertainties in dose-incidence relationships for radiation-induced cancer in animal studies, a number of important generalization have emerged from the extensive laboratory data available. The incidence of cancer is increased by irradiation; the dose-response curve rises with dose up to a certain dose level, above which it may reach a plateau and turn downward with further increase in dose. In the dose range over which the incidence increases with dose, low-LET radiations are usually more effective per cSv at high doses and high dose rates than at low doses and low dose rates. In the same dose range, however, high-LET radiations are usually more effective per cSv than low-LET radiations. For high-LET radiations, the effectiveness is influenced less by dose and dose rate, and in some instances, protraction may increase their effectiveness. The RBE of high-LET radiations tends to increase with decreasing dose and dose rate (1-7). Because of wide species differences in response in laboratory animals, the cancer dose-incidence response for any species cannot provide a reliable basis for direct quantitative risk estimates for cancer-induction in man. Furthermore, variations in the shapes of dose-incidence curves for different radiation-induced neoplasms in laboratory animals confound extrapolation from one type of neoplasm to another, from any one set of exposure conditions to another, or from any one animals specials to another, and particularly to man. ¶ RBE 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; the pattern of energy deposited depends strongly on the quality of radiation (7,8). Different LET radiations are known to cause different numbers of biological effects for the same absorbed dose. Therefore, the microdosimetric distribtion of energy absorption in a defined localized volume within a vital structure, eg, DNA or 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 radiant energy or dose-absorption within a localized volume within the cell to LET (7,8). 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. 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.

DOSE-RESPONSE MODELS: EXTRAPOLATION FROM HIGH-DOSE HUMAN DATA TO LOW DOSES. ¶ Because of the difficulty of obtaining reliable cancer-incidence data in laboratory animals and in humans for low-doses for purposes of risk estimation in exposed human populations dose-response relationships observed at high doses must necessarily be extrapolated into the low-dose region, where human epidemiological data are not available. It is impossible to ascertain the true shape of the dose-effect curve at low-dose levels, and therefore the mechanism of radiation action in the low-dose region cannot be determined (1). Consideration of the spatial and temporal distribution of ionizations suggests that at very low doses, the probability of interaction of ionizing events is negligible. Here, the molecular and cellular response to radiation at very low doses must be linear with dose, irrespective of the shape of the dose-response curve at higher doses. It is reasonable, as well, that the dose-response relationship for cancer incidence at very low doses will be linear, irrespective of the complexity of the carcinogenic process. ¶ Because of uncertainties in epidemiological studies, serious limitations

exist in obtaining reliable and relevant human data, particularly for cancer induction in human populations exposed over a wide range of radiation doses, dose rates, and LET. And, because of these limitations, experimental animal studies must provide essential information; however, human risk estimation cannot be based directly on laboratory animal data. Nevertheless, the evidence suggests that mechanisms of cancer induction in man are similar to those in laboratory animals. It follows, therefore, that while experimental animal data are not quantitatively or directly applicable to man, dose-response relationships in animal studies may be considered for application to human populations exposed to low-level radiation (5,6,9). ¶ 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 (5,9,10). 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 cGy, and α_0, α_1, α_2, β_1 and β_2 are non-negative constants. 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 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 od dose-incidence curves for cancer-induction in irradiated populations, both in animals and in humans, 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 multicomponent quadratic form with a linear term and with an exponential modifier (1,5,6,9,10).

RISK PROJECTION MODELS. Insofar as the cancer incidences and

the radiation doses in exposed human populations are concerned, every effort has been made to ascertain these with the greatest reliability in human epidemiological surveys. But problems arise, particularly in attempts to reconstruct the events of exposure occurring many years previously. The matter of the long latent periods for cancer induction in man complicates our understanding of how to project into the future the risk of cancer induced in individuals exposed in the past or at the present time—that is, the risk 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 were used in the 1980 BEIR-III Report (1) and the 1977 UNSCEAR Report (2)—the absolute risk model and the relative risk model. 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, ie, after the minimum latent period, and continues at an excess rate for a further period, the period of expression. For leukemia, the minimal latent period may be taken as 2-3 years, and the period of expression as 25 years. For solid tumors the minimal latent period may be 10-15 years, and the period of expression 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 of 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. Therefore, 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, 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 ascertained with reasonable accuracy. 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 he 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 risk 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. Eg, it is not known how this affects exposure of children or the fetus in utero (1). ¶ The epidemiological evidence does not favor one risk 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 cancer risk, once expressed in the exposed population, projections into the future either as a relative risk or an absolute risk. The assumptions in the calculations 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. It may very well be that neither risk projection model is valid or appropriate for radiation-induced cancer in man.

THE BEIR III REPORT. 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. 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).

In general, the majority of the Committee preferred linear-quadratic dose-respnse relationships for cancer-induction in human populations exposed to low-dose, low-LET, whole-body irradiation. These are believed to be perhaps the best description for most, but not all, solid tumors induced by radiation. However, because of the numerous uncertainties, the Committee

provided a range or envelope of risk estimates, derived from linear the linear-quadratic and the 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 hyman 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 (1). 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). 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, 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). ¶Thus, we must conclude that numerical estimation of the risk of radiation-induced cancer in man must necessarily be based primarily on human dose-incidence data obtained from epidemiological surveys. However, risk estimation at very low doses and dose rates at present must also necessarily depend on extrapolation from observations at higher doses and higher dose rates, based on assumptions about the dose-incidence relationships and the mechanisms of carcinogenesis. Improvements in our knowledge of the carcinogenic effectiveness of ionizing radiations will depend on the elucidation of mechanisms of carcinogenesis, especially at the very earliest stages of malignant transformation, and on the provision of empirical dose-incidence data for low doses both in human populations and in laboratory animal experiments insofar as this is possible.

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 limitation (11) presently employed, and both had their genesis in the BEIR-I Committee's deliberations (3). ¶First, in the consideration of members low-level radiation exposure of members of the public and public policy, will radiation health effects be expected to occur at

dose levels occurring from annual exposure of 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, and may, in fact, underestimate them when high-dose data are in the cell-killing dose region. ¶ Second, for the radiation worker population exposed to low-level radiation in industry and medicine, will delayed or late health effects occur at levels of annual exposure in the range of 5 to 50 mSv? Here the BEIR-III Committee concluded delayed health effects could occur in those radiations workers with lifetime occupational exposures which may be accumulated by continuously working close to the recommended dose limits, ie, to the maximum permissible dose. ¶ 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 on radiation and health 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 hunan 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 limitation does not necessarily depend on accurate or precise definition of risk. 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 policy in radiation protection, 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 every day life.

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