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Risk estimation and decision making: The health effects on populations of exposure to low levels of ionizing radiation

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Introduction

My assignment this morning is to try to give you some general background for an understanding of the potential health effects in populations exposed to low-level radiation. To do this, I have decided to place our discussions within the framework of the scientific deliberations and the scientific controversies that arose during the preparation of the current Report[1] of the Committee on the Biological Effects of Ionizing Radiation of the National Academy of Sciences-National Research Council (1980 BEIR-III Report). I shall try to explain how certain of the areas addressed by the present BEIR Committee[a] have attempted to deal with the scientific basis for establishing appropriate radiation protection guides, and what effect this may have on evaluation of radiation risks and on decision-making for the regulation of societal activities concerned with the health effects in human populations exposed to low-level radiation. I speak only as an individual on what I consider important in these discussions, and in no way do I speak for the BEIR Committee, or for any of its members, whose deliberations are now available as a comprehensive report: The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980.[1] It would be difficult for me not to be somewhat biased in favor of the substance of the BEIR Reports,[1-3] since as an individual I have been sufficiently close to the ongoing scientific deliberations of agreement and disagreement as they have developed over the past 10 years.

I think it would be best for me to review, very briefly, why we have advisory committees on radiation, and why the BEIR Committee, and its current Report,[1] may be somewhat different than the others. I shall discuss what we know and what we do not know about the health effects of low-level radiation. Further, I shall comment on how the risks of radiation-induced cancer and genetically-related ill-health in man may be estimated, the sources of the scientific and epidemiological data, the dose-response models used, and the uncertainties which limit precise estimates of excess risks from radiation. Finally, I should like to conjecture with you on what lessons we have learned from the BEIR-III Committee experience, and especially on what the implications might be of numerical risk estimation for radiation protection and decision-making for public health policy.

What is the purpose of advisory committees on radiation and health?

For more than three-fourths of a century, scientific and medical observations have led to responsible public awareness of the potential health effects of ionizing radiations, initially from medical and industrial exposure, then from nuclear weapons and weapons testing, and now from the production of nuclear energy. Such awareness has called for expert scientific advice and guidance for protection of the public health. Advisory committees on radiation of international and national scientific composition have, for these many years, met and served faithfully and effectively to discuss, to review, to evaluate, and to report on three important matters of societal concern: 1) to place into perspective the actual and potential harm to the health of man and his descendants in the present and in the future from those societal activities involving the use of ionizing radiations; 2) to develop quantitative indices of harm based on dose-response relationships to provide a scientific basis for the evaluation of somatic and genetic risk so as to better protect human populations exposed to low-level radiation; and 3) to identify the sources and levels of radiation which could cause harm, to assess their relative importance, and to provide a framework on how to reduce unnecessary radiation exposure to human populations.

To a greater or lesser extent, each advisory committee on radiation — such as the UNSCEAR,[b] the ICRP,[c] the NCRP,[d] the NRPB,[e] and others in France,

[a] Committee on the Biological Effects of Ionizing Radiation, National Academy of Sciences-National Research Council, Washington, D.C., USA

[b] United Nations Scientific Committee on the Effects of Atomic Radiation, United Nations, New York, U.S.A.

Canada, and elsewhere in Europe and Japan, and the BEIR Committee — have dealt with these matters. But significant differences occur in the scientific reports of these various bodies. We should expect differences to occur because of the charge, scope, and composition of each committee, and probably most important, because of public attitudes existing at the time of the deliberations of that particular committee, and at the time of the writing of that particular report. The BEIR Report[1] is different. However, the main differences are not so much due to new experimental or epidemiological data or new interpretations of existing data, but rather because of philosophical approach and appraisal of existing and future radiation protection. This results from an atmosphere of constantly changing societal conditions and public attitudes.

Why is the 1980 BEIR-III[1] report different?

The Report[1] of the Committee on the Biological Effects of Ionizing Radiation is the record of the deliberations of an expert scientific advisory committee of the National Academy of Sciences-National Research Council. It deals with the scientific basis of the health effects in human populations exposed to low levels of ionizing radiation. The 1980 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 delayed or late health effects of low-level radiation; 2) It evaluates and analyzes these late health effects — both somatic and genetic — in relation to the risks to health from exposure to low-level radiation. The Committee consisted 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 of the BEIR Committee[1-3] have, in the past, become valuable texts for the scientific basis for development of appropriate and practical radiation protection standards and for decision-making for public health policy.

The 1972 BEIR-I Report[2] and the 1980 BEIR-III Report[1] may differ from one or more of the other radiation advisory committee reports of the UNSCEAR,[4,5] the ICRP,[6,7] the NCRP,[8,9] and of other national councils and committees, in a number of important ways.

First, the BEIR Reports[1-3] are fashioned and written as readable, usable scientific documents for those societal activities concerned with radiation health. The conclusions, recommendations, and detailed appendices are written in a straightforward scientific manner, to be read and understood by scientists, physicians, and government decision-makers alike.

Second, the BEIR Committee[1-3] does not set radiation standards or public health policy. The committee's report are presented to be useful to those responsible for the evaluation of risks and for decision-making concerning regulatory programs and public health policy involving radiation. There is no intent to set the direction for those decision-makers who must consider the strengths and limitations of science and technology along with the relevant societal and economic conditions in the development and execution of such regulatory programs. In this regard, the BEIR Reports[1-3] suggest that those responsible for setting radiation protection standards take into account the current societal needs, so that such standards establish levels of radiation exposure which reflect society's needs at any given time — particularly for general population and occupational exposure from medical applications and from nuclear energy — not necessarily those which are absolutely safe.

Third, available epidemiological surveys and laboratory animal data are reviewed and assessed for their value in estimating numerical risk coefficients for late health effects — particularly cancer and genetically related ill-health — in human populations exposed to low-level radiation. Therefore, the BEIR Reports[1,2] use a practical format for decision-makers. The numerical risk coefficients estimated are presented in terms of probability, with probable upper and lower boundaries derived solely from the scientific facts, epidemiological and experimental data, and the scientific hypotheses and assumptions on which they are based.

Finally, the BEIR Reports[1-3] address the continued need to assess and evaluate both the benefits and risks from those activities involving radiation. In our society, such assessment is essential for societal decision-making when establishing appropriate and achievable radiation protection standards based on risk evaluation. Decisions can and must be made about the value and cost of technological and societal programs for risk reduction by decreasing levels of radiation exposure. This includes decisions concerning alternative methods involving nonradiation activities, comparing their costs to human health and to the environment[3] with other methods.

What are the important biological effects of low-level radiation?

Here, I shall discuss primarily those delayed or late health effects in humans following exposure to low-LET radiation,* X rays, and gamma rays from radioactive sources, and, to a much lesser extent, to high-

[c] International Committee on Radiological Protection, Sutton, Surrey, England.

[d] National Council on Radiation Protection and Units, Washington, D.C., U.S.A.

[e] National Radiological Protection Board, United Kingdom, Harwell, Oxon, England.

*(linear energy transfer)

LET neutron and alpha radiations, since these are the ionizing radiations most often encountered in the nuclear industry and in medicine. Briefly, low-level radiation can affect the cells and tissues of the body in three important ways.

First, if the macromolecular lesion occurs in one or a few cells, such as those of the blood-forming tissues, the irradiated cell can occasionally transform into a cancer cell, and, after a period of time, there is an increased risk of cancer developing in the exposed individual. This biological effect is carcinogenesis; and the health effect, cancer. Second, if the embryo or fetus is exposed during gestation, injury can occur to the proliferating and differentiating cells and tissues, leading to abnormal growth. This biological effect is teratogenesis; and the health effect, developmental abnormality in the newborn. Third, if the macromolecular lesion occurs in the reproductive cell of the testis or the ovary, the hereditary genome of the germ cell can be altered, and the injury can be expressed in the descendants of the exposed individual. This biological effect is mutagenesis; and the health effect, genetically related ill-health.

There are a number of other important biological effects of ionizing radiation, such as induction of cataracts in the lens of the eye or impairment of fertility, but these three important late effects — carcinogenesis, teratogenesis and mutagenesis — stand out as those of greatest concern. This is because a considerable amount of scientific information is known from epidemiological studies of exposed human populations and from laboratory animal experiments. Furthermore, we believe that any exposure to radiation, even at low levels of dose, carries some risk of such deleterious effects. And as the dose of radiation increases above very low levels, the risk of these deleterious health effects increases in exposed human populations. It is these latter observations that have been central to the public concern about the potential health effects of low-level radiation, and to the task of estimating risks and of establishing standards for protection of the health of exposed populations. Indeed, all reports of expert advisory committees on radiation are in close agreement on the broad and substantive issues of such health effects.

What is known about the important health effects of low-level radiation?

A number of very important observations on the late health effects of low-level radiation have now convincingly emerged, about which there is general agreement. These observations are based primarily on evaluation of epidemiological surveys of exposed human populations, on extensive research in laboratory animals, on analysis of dose-response relationships of carcinogenic, teratogenic and genetic effects, and on known mechanisms of cell and tissue injury *in vivo* and *in vitro*.

First, cancer-induction is considered to be the most important late somatic effect of low-dose ionizing radiation. Solid cancers arising in the various organs and tissues of the body, such as the female breast and the thyroid gland, rather than leukemia, are the principal late effects in individuals exposed to radiation. The different tissues appear to vary greatly in their relative susceptibility to cancer-induction by radiation. The most frequently occurring radiation-induced cancers in man include, in decreasing order of susceptibility: the female breast; the thyroid gland, especially in young children and in females; the blood-forming tissues; the lung; certain organs of the gastrointestinal tract; and the bones. Influences affecting the cancer risk include: age at the time of irradiation, and at the time of expression of the disease, sex, and radiation factors and types — LET and RBE — affecting the cancer risk.

Second, the effects of growth and development in the irradiated embryo and fetus are related to the gestational stage at which exposure occurs. It appears that a threshold level of radiation dose and dose rate may exist below which gross teratogenic effects will not be observed. However, these dose levels would vary greatly depending on the particular developmental abnormality and on the radition types and qualities.

Third, estimation of the radiation risks of genetically related ill-health are based mainly on laboratory animal observations — primarily from laboratory mouse experiments — because of the paucity of data on exposed human populations. Our knowledge of fundamental mechanisms of radiation injury at the genetic level is far more complete than, for example, of mechanisms of radiation carcinogenesis, thereby permitting greater assurance in extrapolating information on genetic mutagenesis from laboratory animals to man. With new information on the broad spectrum and incidence of genetically related ill-health in man, such as mental retardation and diabetes, the risk of radiation mutagenesis in man affecting future generations takes on new and special consideration.

What is not known about these health effects of low-level radiation?

In spite of a thorough understanding of these late health effects in exposed human populations, there is still a considerable amount we do not know about the potential health effects of low-level radiation.

First, we do not know what the health effects are at dose rates as low as a few hundred millirem per year, that is, a few factors above natural background radiation exposure. It is probable that if any health effects do occur, they will be masked by environmental or

other competing factors that produce similar health effects.

Second, the epidemiological surveys of exposed human populations are highly uncertain in regard to the forms of the dose-response relationships for radiation-induced cancer in man. This is especially the case for low-level radiation. Therefore, it has been necessary to estimate human cancer risk from low radiation doses primarily from observations of relatively high doses, frequently greater than 100 rads. Estimates of the cancer risk at low doses appears to depend more on what is assumed about the mathematical form of the dose-response function than on the available epidemiological data. However, it is not known whether the excess cancer risk observed at high-dose levels also applies to low-dose levels.

Third, we do not have reliable methods for estimating the repair of injured cells and tissues of the body exposed to very low doses and dose rates. And further, we do not know how to identify those persons who may be particularly susceptible to radiation injury, perhaps on the basis of genetic predisposition.

We also have only very limited epidemiological data on the precise radiation doses absorbed by the tissues and organs of persons in irradiated populations exposed in the past. Furthermore, we do not know the complete cancer incidence in each study population, since new cases of cancer continue to appear with the passing of time. Accordingly, any estimation of excess cancer risk based on such limited dose-incidence information must necessarily be incomplete, until the entire study population has died from natural or other causes.

Finally, we do not now know the role of competing environmental and other host factors — biological, chemical or physical — existing at the time of exposure or following exposure, which may influence and affect the carcinogenic, teratogenic, or genetic effects of low-level radiation.

What are the uncertainties in the dose-response relationships for relation-induced cancer?

In recent years, a general hypothesis for estimation of excess cancer risk in irradiated human populations, based on theoretical considerations, extensive laboratory animal studies, and limited epidemiological surveys, suggests various and complex dose-response relationships between radiation dose and observed cancer incidence.[10-15] Among the most widely considered models for cancer-induction by radiation, based on available information and consistent with both knowledge and theory, takes the complex quadratic form: $I(D) = (a_0 + a_1D + a_2D^2) \exp(-b_1D-b_2D^2)$, where I is the cancer incidence in the irradiated population at radiation dose D in rad, and a_0, a_1, a_2, b_1 and b_2 are non-negative constants (Figure 1).

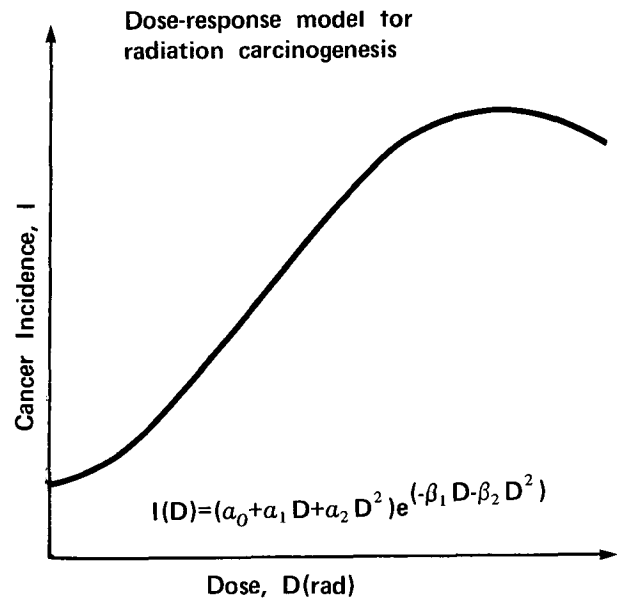

Figure 1. Dose-response model for radiation carcinogenesis.

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 is generally considered to represent the competing effects of biochemical and molecular processes at the subcellular level, leading to cell-killing at high doses. a_0 is the ordinate intercept of 0 dose, and defines the natural incidence of cancer in the population. a_1 is the initial slope of the curve at 0 dose, and defines the linear component in the low-dose range. a_2 is the curvature near 0 dose, and defines the upward-curving quadratic function of dose. b_1 and b_2 are the slopes of the downward-curving function in the high-dose range, and define the processes involved in 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.[1] However, the extent of the variations in the shapes of the dose-response curves derived from the epidemiological or experimental data does not permit direct determination of any of these precise parameter values, or even of assuming their values, or of assuming any fixed relationship between two or more of these parameters. Furthermore, in the case of the epidemiological surveys, this complex general dose-response form cannot be universally applied. Therefore, it has become necessary to simplify the model by reducing the number of parameters which have the least effect on the form of the dose-response relationship in the low-dose range. Such simpler models, with increasing complexity, include the linear, the pure quadratic, the quadratic (with a linear term), and

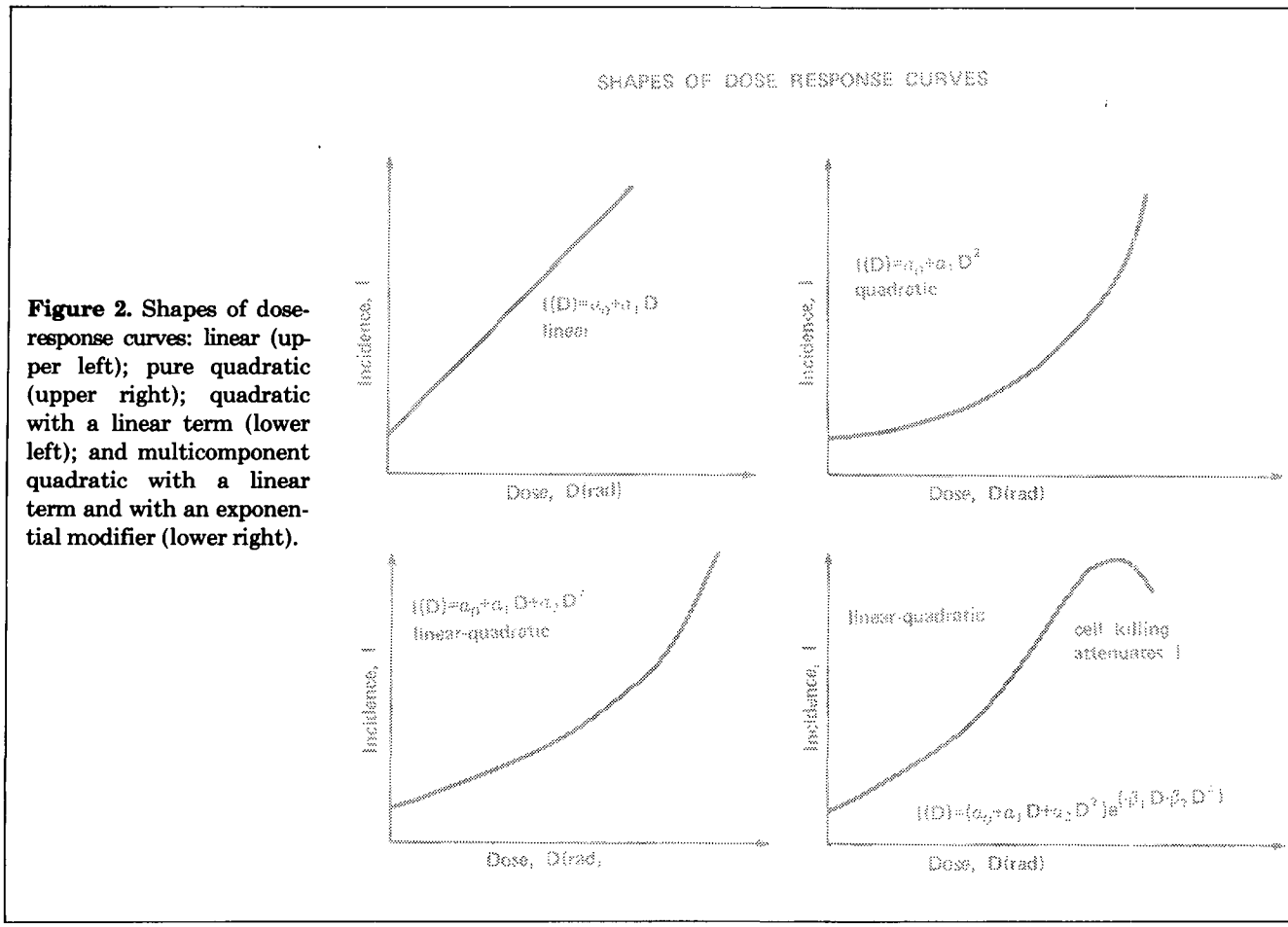

Figure 2. Shapes of dose-response curves: linear (upper left); pure quadratic (upper right); quadratic with a linear term (lower left); and multicomponent quadratic with a linear term and with an exponential modifier (lower right).

finally, the multicomponent quadratic form with a linear term and with an exponential modifier (Figure 2).

Three limitations constrain precise numerical estimation of excess cancer risks of low-level radiation in exposed human populations. First, we lack an understanding of the fundamental mechanisms of cancer-induction by radiation. Second, the dose reponse 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. Nevertheless, these limitations do not relieve decision-makers of the responsibility for guiding public health policy based on appropriate radiation protection standards. Accordingly, not only is it essential that quantitative risk estimation be calculated, based on the available epidemiological and radiobiological data, but in addition, for any authoritative committee report, such as for the current BEIR-III Report,[1] it is equally essential that precise explanations and qualifications of the assumptions, procedures, and limitations involved in the calculation of such risk estimates must be clearly provided.

This has been done explicitly, but not without much discussion and disagreement among the Committee members, in the current BEIR-III Report[1] containing the estimates of excess cancer risk. In its final analyses, the majority of the members of the BEIR 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 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 is the controversy over low-level radiation?

The estimation of the cancer risk of exposure to low-level radiation is said to be clouded by scientific dispute. In particular, there appears to be disagreement among some scientists as to the effects of very

low levels of radiation, even as low as our natural radiation background. Some say this was the central issue of controversy within the BEIR-III Committee, which had been highlighted in scientific periodicals, such as *Nature* and *Science,* and in the news media, such as *The New York Times.*

While there is no precise definition of low-level exposure, many scientists would generally agree that low-level radiation is that which falls within the dose range considered permissible for occupational exposure. According to accepted standards,[16] 5 rem per year to the whole body would be an allowable upper limit of low-level radiation dose for the individual radiation worker. With this as the boundary condition for occupational exposure, it could very well be concluded that most of the estimated delayed cancer cases which might be associated with a hypothetical nuclear reactor accident, or even long periods of occupational exposure among radiation workers, would be considered by some scientists to be caused by exposures well below these allowable occupational limits. Furthermore, if it is assumed that any extra radiation above natural background, however small, causes additional cancer; some extra cancers will inevitably result if millions of people are exposed. Other scientists strongly dispute this, and firmly believe that low-level radiation is nowhere near as dangerous as their colleagues contend. Central to this dispute is the fact 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 just this type of controversy that was at the root of the division among scientists within the 1980 BEIR-III Committee.[17,18] 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 the limited number of 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 earlier 1972 BEIR-I Report[2] had done, some scientists of the 1980 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. 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 could force the U.S. Environmental Protection Agency to adopt stricter health standards to protect against occupational and general population exposure for one example. Other scientists in the Committee did not accept this position, and believe this was an alarmist approach. When there is no human epidemiological evidence at low doses of low-LET radiation, these scientists preferred to assume that the risks of causing cancer are proportionally lower.

Let us look at some of the problems. In its deliberations, the BEIR-III Committee concluded two important observations: 1) It was not yet possible to make precise low-dose estimates for cancer-induction by radiation because the level of risk was so low that it could not be observed directly in man; and 2) there was great uncertainty as to the dose-response function most appropriate for extrapolating to the low-dose region. In studies of exposed animal and human populations, the shape of the dose-response relationships for cancer-induction at low doses may be practically impossible to ascertain statistically. This is because the population sample sizes required to estimate or test a small absolute cancer excess are extremely large. Specifically, the required sample sizes are approximately inversely proportional to radiation dose, and if 1,000 exposed and 1,000 control persons are required in each group to test this cancer excess adequately at 100 rads, then about 100,000 in each population group are required at 10 rads, and about 10,000,000 in each group are required at 1 rad. Thus, it appears that experimental evidence and theoretical considerations are much more likely than empirical epidemiological data to guide the choice of a dose-response function for cancer-induction.

In this dilemma and after much disagreement among some of its members, the majority of the members of the 1980 BEIR-III Committee chose to adopt as a working model for low-dose, low-LET radiation and carcinogenesis the linear quadratic (i.e., a quadratic function with a linear term in the low-dose region) dose-response form with an exponential term to account for the frequently observed turndown of the curve in the high-dose region. However, in applying this multicomponent model, only certain of its derivatives, including the linear, the linear-quadratic, (i.e., the quadratic with linear term), and the pure quadratic functions, could prove practical for purposes of estimation of cancer risk (Figure 2). For the final report, in estimating the excess cancer risk from low-dose low-LET radiation, a majority of the BEIR-III Committee members preferred the linear-quadratic dose-response model, felt to be consistent with epi-

demiological and radiobiological data, in preference to more extreme linear or pure quadratic dose-response models.

In the 1972 BEIR-I Report[2] the cancer risk estimates for whole-body radiation exposure were derived from linear model average excess cancer risk per rad observed at doses generally of a hundred or more rads. These risk estimates were generally criticized on the grounds that the increment in cancer risk per rad may well depend on radiation dose, and that the true cancer risk at low doses may therefore be lower or higher than the linear model predicts.[9] In laboratory animal experiments, the dose-response curves for radiation-induced cancer can have a variety of shapes. As a general rule, for low-LET radiation, the slope of the curve increases with increasing dose. However, at high doses, the slope often decreases and may even become negative. Dose-response curves may also vary with the kind of cancer, with animal species, and with dose rate. On the basis of the experimental evidence and current microdosimetric theory, therefore, the current BEIR-III Committee could quite reasonably adopt as the basis for its consideration of dose-response models the quadratic from with a linear term in the low-dose region, and with an exponential term for a negative slope in the high-dose region (Figure 1).

On the other hand, in large part, the available human data from the large body of epidemiological studies fail to suggest any specific dose-response model, and are not sufficiently 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.[19] Dose-response relationships for the Nagasaki leukemia data appear to have positive curvature.[20] The incidence of breast cancer induced by radiation seems to be adequately described by a linear dose-response mode.[11,21]

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 strongly favored the linear model, others favored the pure quadratic form.[17,18] A further modification of the linear-quadratic form was assumed with the linear and quadratic components to be equivalent at some dose — which was consistent with the epidemiological data and the radiobiological evidence — and avoided dependence on either of the two extreme forms.[14-16]

What are the uncertainties in estimation of the carcinogenic risk in man of low-level radiation?

The quantitative 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. Uncertainties are also 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 diminishes the credibility of 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 preliminary at best, 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 including adequate control groups. There is impressive 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 dose levels, and constraints on data from control groups.

The most reliable and consistent data have been those of the risk of leukemia which come from; the Japanese atomic bomb survivors,[20] the ankylosing spondylitis patients treated with X-ray therapy in England and Wales,[22,23] the metropathia patients treated with radiothrapy for benign uterine bleeding,[24] the tinea capitis patients treated with radiation for ringworm of the scalp,[25,26] and early radiologists.[35] There is evidence of an age-dependence and a dose-dependence, a relatively short latent period of a few years, and a relatively short period of expression, some 10 years. This cancer is almost always fatal.

The epidemiological 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,[27] children treated to the scalp for tinea capitis,[25,26] and the Japanese atomic bomb survivors[20] and Marshall Islanders[28] exposed to nuclear explosions. There is an age-dependence and a sex-dependence — children and females appear to be 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 about 5% of the radiation-induced thyroid tumors are fatal.

The epidemiological surveys on radiation-induced breast cancer in women[13,21] primarily include women with tuberculosis who received frequent fluoroscopic examinations for artificial pneumothorax,[29] postpartum mastitis patients treated with radiotherapy,[30] and the Japanese atomic bomb survivors in Hiroshima and Nagasaki.[20] There is an age-dependence and dose-dependence, as well as a sex-dependence, and the latent period is long, some 20 to 30 years. About half of these neoplasms are fatal.

The epithelial lining of the bronchus and lung is a complex tissue as regards radiation dose involving parameters of the special physical and biological characteristics of the radiation quality. The epidemiological surveys include the Japanese atomic bomb survivors,[20] the uranium miners in the United States and Canada,[31,32] and the ankylosing spondylitis patients in England and Wales.[22,23] There is some evidence of an age-dependence from the Japanese experience, and relatively long latent period. This cancer is almost always 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,[33,34] is low. For all other tumors arising in various organs and tissues of the body, values are extremely crude and estimates are preliminary at best.

There is now a large amount of epidemiological data from comprehensive surveys from a variety of sources. These data indicate that leukemia is no longer the major cancer induced by radiation — that solid cancers are exceeding the relative incidence of radiation-induced leukemia.[5] That is, in view of the long latent period after some 30 years or more following radiation exposure, the risk of excess solid cancers is many times the risk of excess leukemia. But these risk estimates must remain very crude at the present time, since they do not take into account any lack of precision in certain of the epidemiological studies, particularly as regards radiation dose distribution, ascertainment, latency periods, and other physical and biological parameters. The BEIR,[1,2] the UNSCEAR,[4,5] and the ICRP[6,7] Reports have estimated the risk from low-LET, whole-body exposure in different ways. Based on the epidemiological surveys carefully followed, with adequate control study populations, a crude figure of the total lifetime absolute risk of radiation-induced cancer deaths can be derived. This estimate for low-LET radiation, delivered at low doses, would be less than about 100 excess cases per million persons exposed per rad. But this figure could very well be an over-estimate of the true risk, and the actual number of excess cancer cases may be much lower.[1,5] Although any such numerical estimate must be considered unreliable, it does provide a very rough figure for comparison with other estimates of avoidable risks, or voluntary risks, encountered in everyday life.

What are the risk estimates of radiation-induced cancer in man?

The chief sources of epidemiological data currently for risk estimation of radiation-induced cancer in man are the Japanese atomic bomb survivors exposed to whole-body irradiation in Hiroshima and Nagasaki,[20] the patients with ankylosing spondylitis [22,23] and other patients who were exposed to partial body irradiation therapeutically,[25-27,29] or to diagnostic radiographs and the various occupationally-exposed populations[31-35] such as uranium miners and radium dial painters. Most epidemiological data do not systematically cover the range of low to moderate radiation doses which are fairly reliable in the Japanese atomic bomb survivor data. Analysis in terms of dose-response, therefore, necessarily rely greatly on the Japanese data. The substantial neutron component of dose in Hiroshima, and its correlation with gamma dose, limit the value of the more numerous Hiroshima data for the estimation of cancer risk from low-LET radiation. The Nagasaki data, for which the neutron component of dose is small, are less reliable for doses below 100 rads.

The 1980 BEIR-III Report[1] 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 approximating conditions of occupational exposure. These three exposure situations were not chosen to reflect any circumstances that would normally occur, but to embrace the areas of concern — general population and occupational exposure, and single and continuous exposure. These dose levels were substantially different from the only exposure situation chosen for the illustrative computation by the 1972 BEIR-I Committee, where 100 mrem per year was the level selected.[2] Some members of the current BEIR-III Committee strongly felt that below

these three dose levels, which were arbitrarily chosen for the 1980 Report,[1] 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 maximum permissible dose for occupational exposure, is nevertheless consistent with the occupational exposure experience in the nuclear industry. The 1969-1971 U.S. life-table was used as the basis for the calculations. The expression time was taken as 25 years for leukemia and the remaining years of life for other cancers. Separate risk estimates were made for cancer mortality and for cancer incidence.

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 dose-response model predicts increases of about 0.5% and 1.4% 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 3% to 8% over the normal expectation, depending on the projection model (Table 1).

Table 2 compares the cancer risk following exposure to 10 rads, calculated according to three different dose-response models, viz., the linear-quadratic, the linear, and the quadratic. 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 between these two extremes.

Table 3 compares the 1980 BEIR-III Report[1] cancer mortality risk estimates with those of the 1972 BEIR-I Report[2] and the 1977 UNSCEAR Report.[5] To do this, it was most convenient to express them as cancer deaths per million persons per rad of continuous lifetime exposure. For continuous lifetime exposure to 1 rad per year, the linear-quadratic dose-response model for low-LET radiation yields risk estimates considerably below the comparable linear-model estimates in the 1972 BEIR-I Report;[2] the dif-

Table 1. Estimated excess mortality per million persons from all forms of cancer, linear-quadratic dose-response model for Low-LET radiation.[1]

	Absolute-Risk Projection Model	Relative-Risk Projection Model
Single exposure to 10 rads:		
Normal expectation	163,800	163,800
Excess cases: number	766	2,255
% of normal	0.47	1.4
Continuous exposure to 1 rad/yr, lifetime:		
Normal expectation	167,300	167,300
Excess cases: number	4,751	12,920
% of normal	2.8	7.7

Table 2. Estimated excess mortality per million persons from all forms of cancer, single exposure to 10 rads of Low-LET radiation, by dose-response model.[1]

Dose-Response Model			Absolute-Risk Projection Model	Relative-Risk Projection Model
Luekemia And Bone	Other Cancer			
		Normal expectation or cancer deaths	163,800	163,800
$\overline{\text{LQ-L}}$	$\overline{\text{LQ-L}}$	Excess deaths: number	766	2,255
		% of normal	0.47	1.4
$\overline{\text{L-L}}$	$\overline{\text{L-L}}$	Excess deaths: number	1,671	5,014
		% of normal	1.0	3.1
$\overline{\text{Q-L}}$	$\overline{\text{Q-L}}$	Excess deaths: number	95	276
		% of normal	0.058	0.17

Table 3. Comparative estimates of the lifetime risk of cancer mortality induced by Low-LET radiation — excess deaths per million, average value per rad by projection model, dose-response model, and type of exposure.[a]

Source of Estimate	Dose-Reponse Models	Projection: Single Exposure to 10 rads — *Absolute*	Projection: Single Exposure to 10 rads — *Relative*	Projection: Continuous Lifetime Exposure to 1 rad/yr — *Absolute*	Projection: Continuous Lifetime Exposure to 1 rad/yr — *Relative*
BEIR, 1980[b]	LQ-L, $\overline{\text{LQ-L}}$	77	226	67	182
1972 BEIR report factors	Linear	117	621	115	568
UNSCEAR 1977	Linear		75-175		

a) For BEIR 1980, the first model is used for leukemia, the second for other forms of cancer. The corresponding estimates when the other models are used (thereby providing an envelope of risk estimates) are:

L-L, $\overline{\text{L-L}}$	167	501	158	430
Q-L, $\overline{\text{Q-L}}$	10	28		

b) The values are average values per rad, and are not to be taken as estimates at only 1 rad of dose.

ferences mainly reflect changes in the assumptions made by the two BEIR Committees almost a decade apart. The 1980 BEIR-III Committee preferred a linear-quadratic rather than linear dose-response model for low-LET radiation, and did not assume a fixed relationship between the effects of high-LET and low-LET radiation (which was based on the Japanese atomic bomb survivor studies). Furthermore, the 1980 BEIR-III Report[1] cancer risk estimates do not, as in the 1972 BEIR-I Report,[2] carry through to the end of life the very high relative-risk coefficients obtained with respect to childhood cancers induced *in utero* by radiation.

There is a good deal of reluctance by some scientists to introduce cancer-incidence data for purposes of radiation-induced cancer risk estimation. Cancer mortality data are considered far more reliable than comparable incidence data, and thus, cancer incidence risk estimates are less firm than mortality estimates. However, the incidence of radiation-induced cancer is considered by many scientists and by decision-makers alike, to provide a more complete expression of the total social cost of radiation-induced cancer in man than does mortality. The 1980 BEIR-III Committee chose to introduce cancer-incidence data for risk estimation for the first time in any report, and also applied a variety of dose-response models and several data sources. For continuous lifetime exposure low-LET, whole-body, 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% to 6%, depending on the projection model. The various dose-response models produced estimates that differed by more than an order of magnitude, whereas the different data sources gave broadly similar results. Risks for females were substantially higher than those for males, due primarily to the relative importance of radiation-induced breast and thyroid cancer.

Estimates of excess cancer risk for individual organs and tissues depend in large part on partial-body irradiation and use a much wider variety of epidemiological data sources. Except for leukemia and bone cancer, estimates for individual sites of cancer can be made only on the basis of the linear model, and all risk coefficients are estimated as the number of excess cancer cases per year per million persons exposed per rad. For leukemia, the linear-quadratic model yielded about 1.0 to 1.4 excess leukemia cases, for females and males respectively. For example linear-model estimates for solid cancers were: for thyroid in males, about 2, and in females, about 6; for female breast, about 6; and for lung, about 4. These risk coefficients derive largely from epidemiological data in which exposure was at high doses. These values may, in some cases, overestimate risk at low doses.

What is known about the teratogenic effects of low-level radiation?

Developing mammals, including man, are particularly sensitive to radiation during their intrauterine and early postnatal life. The developmental effects of radiation on the embryo and fetus are strongly related to the stage at which exposure occurs. Most information comes mainly from laboratory animal studies, but the human data are sufficient to indicate qualitative correspondence for developmentally equivalet stages.[1,37-41]

Radiation during preimplantation stages probably produces no abnormalities in survivors, owing to the great developmental plasticity of very early mammalian embryos. Radiation at later stages may, however, produce morphologic abnormalities, general or local growth retardation, or functional impairments, if doses are sufficient. Obvious malformations are particularly associated with irradiation during the period of major organogenesis, which in man extends approximately from the second through the ninth week from

conception. More restricted morphologic and functional abnormalities and growth retardations dominate the spectrum of radiation effects produced during the fetal and early postnatal periods. Some of these effects can be apparent at birth, and others may show up later; and subtle functional damage cannot be adequately measured with available techniques.

Because the central nervous system is formed during a relatively long period in human development, such abnormalities as microcephaly and mental retardation figure prominently among the list of radiation effects reported in man.

In laboratory animals, developmental abnormalities (CNS injury and oocyte killing) have been observed at doses below 10 rads.[40] The experimental data can be used with some confidence to fill in gaps in the human experience, particularly with respect to extrapolations to low exposure levels, where it is very difficult to obtain direct evidence in human populations. Atomic-bomb data for Hiroshima show that the frequency of small head size was increased by acute air doses in the range of 10-19 rads kerma (average fetal dose, gamma rays at 5 rads plus neutrons at 0.4 rad) received during the sensitive period, and suggest that it was also increased in the 1-9 kerma range (average fetal dose, 1.3 rads gamma plus 0.1 rad neutrons). At Nagasaki, where almost the entire kerma was due to gamma rays, there was no increase in the frequency of small head size at air doses below 150 rads kerma.[38]

Because a given gross malformation or functional impairment probably results from damage to more than a single target, the existence of a threshold radiation dose below which that effect is not observed may be predicted. There is evidence of such thresholds, but they vary widely, depending on the abnormality. Lowering of the dose rate diminishes the damage. Furthermore, exposure protraction can reduce dose effectiveness by decreasing to below the threshold the portion of the dose received during a particular sensitive period.

What is known about the genetic effects of low-level radiation?

Because radiation-induced transmitted genetic effects have not been demonstrated in man, and because of the likelihood that adequate information will not soon be forthcoming, estimation of genetic risks must be based on laboratory animal data. This entails the uncertainty of extrapolation from the laboratory mouse to man. However, there is information on the nature of the basic lesions, which are believed to be similar in all organisms. Some of the uncertainties in the evaluation of somatic effects are absent in the estimation of genetic risk.[1,42-45]

The genetic disorders that can result from radiation exposure are: 1) those which depend on changes in individual genes (gene mutations or small deletions); and 2) those which depend on changes in chromosomes, either in total number or in gene arrangement (chromosomal aberrations). Gene mutations are expected to have greater health consequences than chromosome aberrations. At low levels of exposure, the effects of radiation in producing either kind of genetic change is proportional to dose. Risk estimates are based either on experimental findings at the lowest doses and dose rates for which reliable data have been obtained or on adjustment of the observed data obtained at high doses and dose rates by a dose-rate reduction factor. For low doses and dose rates, a linear extrapolation from fractionated-dose and low-dose-rate laboratory mouse data continues to constitute the basis for estimating genetic risk to the general population.[1,2] Genetic-risk estimates are expressed as effects per generation per rem, with appropriate corrections for special situations, such as exposures of small groups to high-LET radiation.

Two methods may used to estimate the incidence of disorders caused by gene mutations.[1] One method estimates the incidence expected after the continuous exposure of the population over a large number of generations. The other method estimates the incidence of disorders expected in a single generation after the exposure of the parents. By the first method, it is estimated that about 1-6% of all spontaneous mutations that occur in humans are due to background radiation. A small increase in radiation exposure above background leads to a correspondingly small relative increase in the rate of mutation. The numerical relationship of rates of induced and spontaneous mutation is relative-mutation-risk factor, that is, the ratio of the rate of mutations induced per rem to the spontaneous rate. The reciprocal of the relative-mutation-risk factor is the "doubling dose," or the amount of radiation required to produce as many mutations as are already occurring spontaneously. The estimated relative mutation risk for humans is 0.02-0.004 per rem (or a doubling dose of 50-250 rem). After many generations of increased exposure to radiation, it is expected that human hereditary disorders that are maintained in the population by recurrent gene mutation would show a similar increase in incidence.

Table 4 lists the current 1980 BEIR-III Report[1] risk estimates of the potential genetic effects of an average population exposure of 1 rem per 30-year generation. In the first generation, it is estimated that 1 rem of parental exposure throughout the general population will result in an increase of 5-75 additional serious genetic disorders per million liveborn offspring. Such an exposure of 1 rem received in each generation is estimated to result, at genetic equilibrium, in an increase of 60-1,100 serious genetic disorders per million liveborn offspring. The ranges of the

Table 4. Genetic effects of an average population exposure of 1 rem per 30-year generation.[1]

Type of Genetic Disorder[a]	Current Incidence in 1 Million Live-born Offspring.	Effect of rem per Generation per Million Liveborn Offspring. *First Generation*[b]	*Equilibrium*[c]
Autosomal dominant and X-linked	10,000		40-200
Irregularly inherited	90,000	5-65	20-900
Recessive	1,100	Very few	Slowly increases
Chromosomal aberrations (congenital malformations)	6,000	Less than 10	Increases slightly

a) Includes diseases that cause serious handicap at some time during lifetime. b) Estimated directly from measured phenotypic damage or from observed cytogenetic effects. c) Estimated by the relative-mutation-risk method.

risk estimates emphasize the limitations of current understanding of genetic effects of radiation on human populations. Within this range of uncertainty, however, the risk is nevertheless small in relation to current estimates of the incidence of serious human disorders of genetic origin — roughly 11% of liveborn offspring, that is, approximately 107,000 cases per million liveborn.

Genetic risk estimates are based on induced disorders judged to cause serious genetic ill-health at some time during life. Some disorders are obviously more important than others. In contrast with somatic effects, which occur only in the persons exposed, genetic disorders occur in descendants of exposed persons and can often be transmitted to many future generations. The major somatic risk estimates are concerned with induced cancers. Although many of these are fatal, some are curable, such as most thyroid cancers, but entail the risk and costs of medical care and disability. Somatic effects also include developmental abnormalities of varied severity caused by fetal or embryonic exposure. Comparisons of genetic and somatic effects must take into account ethical or socioeconomic judgments. It is extremely difficult to compare the societal impact of a cancer with that of a serious genetic disorder.[1]

What are the implications of numerical risk estimation and decision-making for radiation protection and public health policy?

In its evaluation of the epidemiological surveys and the laboratory animal data, the national and international committees on radiation carefully review and assess the value of 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 necessarily and understandably lead to some disagreement not only outside the committee room, but among committee members as well. But such disputes and disagreements center not on scientific facts and not on 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 draw some firm conclusions on which to base scientific public health policy for radiation protection standards. The setting of any permissible radiation level or guide for low-level exposure remains essentially an arbitrary procedure. Any lack of precision minimizes neither the need for setting responsible public health policies, nor the conclusion that such risks are extremely small when compared with alternative options, and those accepted by society as normal everyday hazards. Since society benefits from the necessary activities of energy production and medical care, it is apparent that it must also establish appropriate standards and controlling procedures which continue to assure that its needs and services are being met with the lowest possible risks.

In a third century of inquiry, including some of the most extensive and comprehensive scientific efforts on the health effects of an environmental agent, much of the important information necessary for determination of radiation protection standards is now becoming available to decision-makers for practical and responsible public health policy. It is now assumed that any exposure to radiation at low levels of dose carries some risk of deleterious health effects. How low the level may be, the probability or magnitude of the risk at very low-levels of dose still are not known and may remain so. Radiation and the public health, when it involves the public health, becomes a broad societal problem and not solely a scientific one. Decisions concerning this problem will be made by society, most often by men and women of law and government. Our best scientific knowledge and our best scientific advice are essential for the protection of the public health, for the effective application of new technologies in medicine and industry, and for guidance in the production of nuclear energy. 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. A pragmatic appraisal of how man wishes to continue to derive the benefits of health and happiness from activities involving ionizing radiation — considering the everchanging public attitudes and our resource-limited society — is the present and future task which lies before each expert advisory committee on the biological effects of ionizing radiation concerned with risk assessment and decision-making.

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