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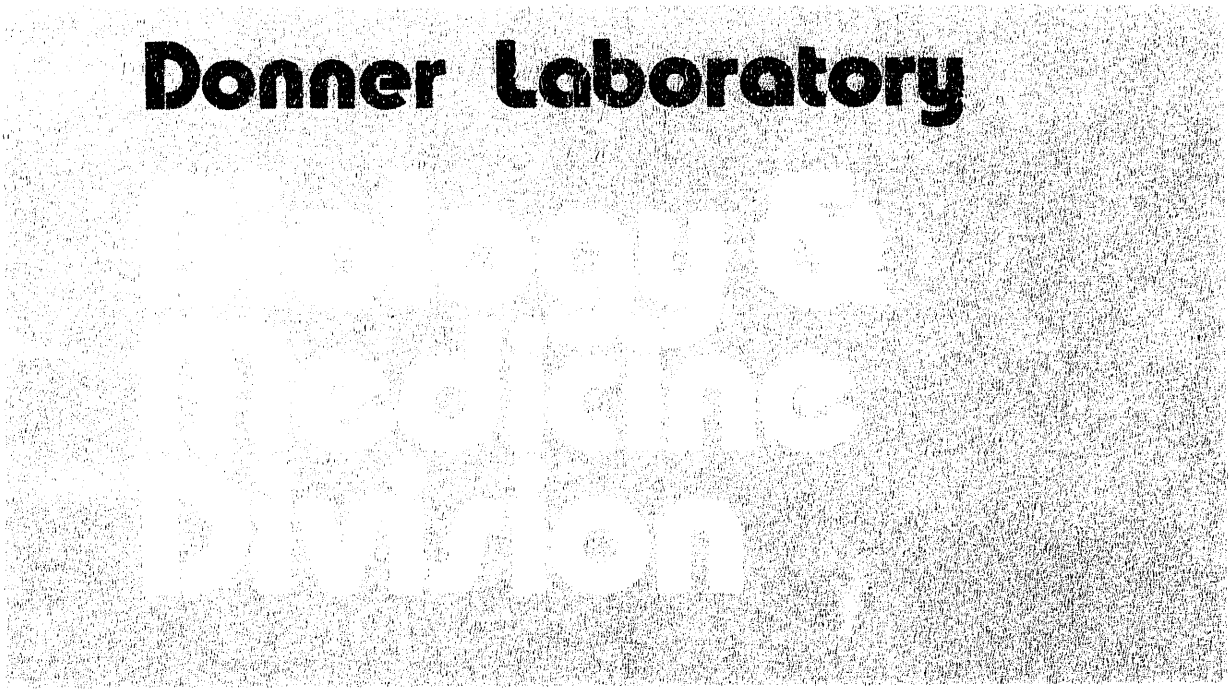

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The Carcinogenic Risks of Low-LET and High-LET Ionizing Radiations

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Abstract

During the past decade, new and important information has become available concerning the carcinogenic effects of radiation and the implications for risk assessment and risk management. This new information comes mainly from further follow-up of the epidemiological studies of the Japanese atomic bomb survivors, patients irradiated medically for cancer and allied conditions, and workers exposed in various occupations. In the Japanese atomic bomb survivors the carcinogenic risks are estimated to be somewhat higher than previously, and this is due to the reassessment of the atomic-bomb dosimetry, further follow-up with increase in the number of excess cancer deaths, particularly in survivors irradiated early in life, and changes in the methods of analysis to compute the age-specific risks of cancer. Overall, the cancer mortality data are now more compatible with the relative risk projection model. Because of the characteristics of the atomic bomb survivor series as regards sample size, age and sex distribution, duration of follow-up, person-years at risk, and type of dosimetry, the mortality experience of the atomic bomb survivors was selected by the 1988 UNSCEAR Committee and the 1990 BEIR V Committee as the more appropriate basis for projecting risk estimates for the general population. In the atomic bomb survivors, the dose-effect relationship for overall cancer mortality other than leukemia is consistent with linearity below 3 Gy, while the dose-effect relationship for leukemia, excluding chronic lymphatic leukemia, conforms best to a linear-quadratic function. The shape of the dose-incidence curve at low doses still remains uncertain, and the data do not rule out the possible existence of a threshold for any neoplasm. The BEIR V Committee developed modified multiplicative risk projection models to project lifetime risk estimates; the preferred models contained dose (and dose squared) terms as well as age at exposure, time since exposure, and interaction effects. In its report, it is estimated that if 100,000 persons received an instantaneous dose of 0.1 Sv of low-LET radiation, about 790 extra cancer deaths would be expected to occur during their remaining lifetime in addition to nearly 20,000 cancer deaths that will occur even in the absence of the radiation; a DREF of 2 or more should be applied to this estimate for cancers other than leukemia, since the linear-quadratic model

applied to leukemia implies a DREF of about 2. If that population were exposed continuously to 1 mSv per year for an entire lifetime, about 560 extra cancer deaths would be expected to occur. The BEIR V Committee concluded that the constant additive risk model for risk estimation is no longer tenable; based on the modified multiplicative risk models for all cancers combined, the current risk estimate reported by the 1990 BEIR V Committee are appreciably higher, by a factor of about 3 to 4, than comparable estimates reported by the 1980 BEIR III Committee.

Opening Statement

Thank you, Mr. President. I extend to you and to your colleagues of the scientific and program committees and to the participants of this 32nd Annual Meeting of the Japan Radiation Research Society, my sincerest appreciation for the very special honor of addressing you today on the carcinogenic effects and risk estimates of low-LET and high-LET radiations. My wife, who is sharing this moment with me, and I are grateful to you for extending your very gracious invitation, and for the memorable hospitality accorded to us. The occasion of our visit, originally recorded as one for scientific interaction, has been changed---it has become an occasion for renewing old friendships, and for creating new ones.

Prologue

I plan at this time to discuss with you certain of the most recent findings of the United States National Academy of Sciences' 1988 BEIR IV Report (1) and the current 1990 BEIR V Report (2), i.e., the most recent report of the Committee on the Biological Effects of Ionizing Radiations which has just completed its final deliberations on the effects of low-level irradiation on human populations. I shall try to place the BEIR V Report (2) in perspective as regards the 1988 BEIR IV Report (1) and the 1988 UNSCEAR Report (3), and bring to you a new set of risk

estimates of the carcinogenic effects of radiation in humans. Because of the time required for the completion of the review process of such a scholarly and detailed report, it is not surprizing that the BEIR V Report (2) underwent extensive preparation for publication and has not as yet been released in its official form by the National Academy of Sciences. This will soon take place.* The proper reservations and boundaries of responsible scientific behavior and good taste allow for some academic license, and I have been permitted for this special occasion to give you certain of its precise numerical estimates at this time. It is not my official charge to do so and I shall refrain from any indiscretion; nevertheless, I can share with you some of the BEIR V Committee's deliberations.

There is a great deal we can discuss today about the recent work of these three committees and the process of risk estimation, and this is my intention. At the outset, I have made three general assumptions. First, it is assumed in radiation risk assessment that the carcinogenic effects of ionizing radiation are stochastic phenomena, that is, lacking thresholds. Second, for protection guidance and risk management, it is assumed that these effects increase in frequency as linear nonthreshold functions of the radiation dose at low doses, and it is the magnitude of the increase per unit dose and the extent to which it may vary with different biological, physical and other variables that remain the subjects of continued scientific inquiry. And third, it is assumed that because of the new and important information on the health effects that has become available during the past decade and their broad significance for revisions of risk estimates, I should confine my remarks to the carcinogenic effects exclusively and to review the salient features of these newer approaches, concepts and data on which they are based. These represent the substance of the most recent committee reports, and have been summarized recently in the UNSCEAR (3,4) and the National Academy of Sciences' BEIR (1,2) reports.

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* The BEIR V Report (2) was released in January 1990.

Introduction

Important new information on human beings has come mainly from further follow-up of existing epidemiological studies, notably the Japanese atomic bomb survivors and the ankylosing spondylitis patients; from new epidemiological surveys, such as the patients treated for cancer of the uterine cervix; and from combined surveys, including workers exposed in underground mines. Since the numerous and complex differences among the different study populations introduce factors that influence the risk estimates derived in ways that are not completely understood, it is not clear how to combine the different risk estimates obtained. These factors involve complex biological and physical variables distributed over time. Because such carcinogenic effects occur too infrequently to be demonstrated at low doses, the risks of low-dose radiation can be estimated only by interpolation from observations at high doses on the basis of theoretical concepts, mathematical models and available empirical evidence, primarily the epidemiological surveys of large populations exposed to ionizing radiation.

In spite of a considerable amount of research, only recently has there been efforts to apply the extensive laboratory data in animals to define the dose-incidence relationship in the low dose region. There simply are insufficient data in the epidemiological studies of large human populations to estimate risk coefficients directly from exposure to low doses. Nevertheless, we must look to the new information on radiation carcinogenesis in exposed human populations---people exposed to nuclear radiations, the Japanese atomic bomb survivors; patients exposed to medical radiations, the ankylosing spondylitics in England and Wales, women treated for carcinoma of the cervix, and children irradiated for *tinea capitis* and for other benign diseases; and workers exposed occupationally, mostly involving internally-deposited alpha-emitters, such as the underground miners and the radium dial painters and chemists. From the new evidence, we may conclude that the risk estimates for the carcinogenic effects of radiation have been, in the past, somewhat low and reassessment of the numerical values is now necessary.

Epidemiological Studies

Japanese Atomic Bomb Survivors. By far, the most important survey contributing to current radiation risk assessment is that of the Japanese atomic bomb survivors. It is this study that provides the greatest amount of information, and frequently the only information, required for reassessment of previous risk estimates. This prospective study involves 76,000 survivors, with internal controls, 59% female and 41% male, with an age distribution of 0 to 90 years. The average period of follow-up to 1985 approaches 29 years, with 2,185,000 person-years at risk. The data are based on the DS86 individual dosimetry on each survivor; the radiation dose was whole-body and instantaneous, and the range of absorbed doses 10 mGy to 6 Gy, with a mean whole-body absorbed dose of 0.24 Gy.

The new data (5) indicate that the carcinogenic effects of atomic radiation in the Hiroshima and Nagasaki survivors---the risk per unit dose---are higher than previously estimated. There are three explanations. First, the reassessment of the *atomic bomb dosimetry*, i.e., the revised DS86 dosimetry, substantially reduces the high-LET neutron component. Second, there is an increase in the number of cancer deaths with continued follow-up that is particularly evident in survivors who were irradiated in early life. Third, there have been changes in the method used to calculate the cancer rate, based on age at risk and time since exposure (6).

The most important contribution of the revision of the atomic-bomb dosimetry concerns the contribution of neutrons to the total dose received by the survivors in both cities; currently this is considered much less significant than previously in the new DS86 system. This results in a higher gamma tissue dose in the Hiroshima survivors, and slightly less in Nagasaki, and permits pooling of the data. The pooling of the Hiroshima and Nagasaki data is now possible since the previously estimated difference in risk per unit dose is no longer statistically significant. Given the lesser amount of neutrons, and assigning a fixed RBE of 10 or more, significantly affects the current risk estimates. Overall the carcinogenic risk per unit dose equivalent is increased some 40 to 70% for solid tumors, and more for leukemia, depending on the tissue at risk and its depth in the body. No

basis remains for estimating the carcinogenic risk of neutron radiation in exposed human populations.

Two *risk projection models* currently used to project an estimate of the overall cancer risk for an exposed population---the *additive* and *multiplicative* models---were examined by the UNSCEAR Committee (3) and the BEIR V Committee (2). Both models are flawed, but since the lifetime cancer experience for low-dose radiation is not yet available for any of the large epidemiological studies, such models suitably modified are necessary. The additive risk projection model assumes that the excess cancer risk is independent of the natural incidence, and that radiation will induce a dose-dependant excess number above the baseline level. The multiplicative model assumes the excess cancer risk is related to the natural incidence, and that radiation will induce a dose-dependent excess percentage above the baseline incidence. The UNSCEAR Committee applied both risk projection models; the BEIR V Committee rejected the additive model, and developed modified multiplicative models. Shimizu et al. (5) have estimated that the cumulative radiation-associated excess of cancer deaths in the Japanese survivors has risen from about 135 in 1975 to about 260 in 1985 for the DS86 cohort. The excess has also increased with attained age, but the excess relative risk has remained reasonably constant. Overall, the excess cancer mortality experience appears much more closely related to the multiplicative model than the additive model, although the reliability of either model for cancer of a specific type or site, or for those persons exposed at a younger age, continues to remain uncertain.

The limited data available to examine the *dose-response relationships* at low doses of low-LET radiation has made it necessary to interpolate from high dose data. The Japanese leukemia data still conform to the nonthreshold linear-quadratic model, whereas for cancer deaths other than leukemia, the data support a nonthreshold linear model in the exposure range below 3 Gy (5). The excess mortality from cancer of various sites has been estimated to be: for leukemia, a relative risk of 6.21 at 1 Gy (organ-absorbed dose), and an absolute risk of 2.94 excess leukemia deaths per 10,000 PYGy; and for all cancers except leukemia, a relative risk of 1.41 at 1 Gy, and an absolute risk of 10.13 excess cancer deaths per 10,000 PYGy (Table 1). Only for leukemia, esophagus,

stomach, large intestine, lung, female breast, ovary, urinary tract, and multiple myeloma were there sufficient data to permit numerical risk estimates to be calculated. Except for the special circumstances of the carcinogenic effects of internally-deposited alpha emitters (1) and for certain selected studies of the thyroid and breast, it has been the mortality experience of the Japanese atomic bomb survivors that was selected in both the 1988 UNSCEAR Report (3) and the 1990 BEIR V Report (2) as the most appropriate basis for projecting risk estimates of carcinogenic effects for the general population.

Ankylosing Spondylitis Patients. The ankylosing spondylitis study (7) is a long-standing retrospective- prospective epidemiological survey of over 14,000 patients with average follow-up of 8.1 years, with 184,000 person-years at risk. Some 83% of the cohort are males; national life rates in the United Kingdom are used for controls. The X-irradiation was fractionated, with non-uniform, partial-body exposure at high doses, a range of 0 to 8 Gy and a mean tissue absorbed dose of about 2 Gy. Dosimetry remains incomplete; it is on an individual basis for leukemia, but a 1 in 15 random sample drawn from medical charts for all other cancers. The study is confounded, in part, by the underlying disease for which the radiation was given therapeutically and the association of certain health outcomes, such as colon cancer. This survey has provided new data on patients followed up to 48 years after a single course of X-ray therapy to the spine (7).

Cancer mortality of several of the heavily irradiated tissues has increased significantly between the 5th and 25th year following irradiation, after which time the excess decreased for certain sites, such as the lung and stomach (Table 2). Whatever the pattern of temporal distribution of excess cancers, it appears that susceptibility to a specific radiation-associated cancer demonstrates no consistent relationship to the spontaneous incidence of the cancer in the general population. This suggests unexplained and complex organ-, tissue-, and cell- dependant differences in susceptibility to radiation carcinogenesis. Overall, the cancer excess per unit dose is less than in the atomic bomb survivors. Dose-response relationships are complicated by the incomplete dosimetry; there are wide variations among different organs and tissues and within any given organ, and are limited by the absence of dose data for individual patients.

Medical Radiation Surveys:. It is primarily from the wide array of epidemiological evidence from medical radiation exposure that support the use of the linear and linear-quadratic extrapolation models of dose-incidence relationships at low doses (2). The evidence includes an excess of childhood leukemia following *in utero* exposure at doses of 10 to 50 mGy; an excess of thyroid tumors at doses of 60 to 80 mGy after childhood exposure for *tinea capitis*; an excess of breast cancer in women exposed to multiple fluoroscopic chest examinations or radiotherapy for benign breast conditions. Since the publication of the 1980 BEIR III Report (8), additional cohort studies have provided data that are consistent with the findings of the atomic-bomb survivors. Individually, no one study provides sufficient information to define the dose-incidence relationships at low doses, but collectively the data from these studies are consistent with a nonthreshold linear function at low doses for each of the carcinogenic effects.

The largest of these studies is the multi-institutional survey of women treated for carcinoma of the cervix, in whom leukemia and cancers of the urinary bladder, breast, kidney, stomach and rectum have occurred in excess (9). This retrospective-prospective study is especially noteworthy; it involves 83,000 women, less than 30 to greater than 70 years of age, an average follow-up of 7.6 years, with 623,800 person-years at risk. The control groups involve national rates and internal controls. The radiation was chronic, fractionated and partial-body exposure to low-LET gamma and X-rays, and the doses were high and with extremely uneven distribution throughout the abdomen and pelvis, approaching 60 Gy to the affected tissues. Currently, the dosimetry is sparse, and represented by the mean dose of a sample population.

Other cohort studies of importance involve children treated for leukemia in whom an excess of brain and other tumors has been observed (10,11); patients treated for Hodgkin's disease in whom cancers of bone and soft tissues, skin, oropharynx, nervous system, respiratory system and digestive tract has been observed in excess (10); patients treated for ovarian cancer in whom uterine, colon, bladder, and hematologic cancers have been observed in excess (12); patients treated with radium-224 for tuberculosis and ankylosing spondylitis in whom an excess of bone cancers has been observed (13); and patients treated for *tinea capitis* in whom thyroid tumors and

intracranial cancers have been observed in excess (14). Although the number of cancers in these study populations are relatively small and the relevant radiation doses too uncertain, and thus not adequate to define the shape of the dose-incidence relationship in the low-dose region, the data from each of these studies are consistent with existing quantitative dose-incidence information derived from the Japanese experience. The last two studies are noteworthy in that the radium-224 patients were exposed to high-LET alpha-emitting bone-seeking radionuclides, and the excess thyroid cancer appeared in the *tinea capitis* cohorts who were exposed to quite small average estimated doses to the thyroid gland. Recent studies extend the observations of childhood cancers observed following *in utero* irradiation; in Connecticut, U.S.A., a study (15) of twins irradiated *in utero* (estimated median dose of 10 mGy) demonstrated a relative risk of 1.6 for leukemia and 3.2 for all childhood cancers, consistent with the study in Great Britain (16), and the expanded multi-institutional New England survey (17).

Occupational Exposure. The studies of underground miners in the United States, Canada, Sweden, and Czechoslovakia, who developed lung cancer after exposure to high levels of alpha radiation from radon progeny in the mines (1,2,18,19) are of considerable importance. The risk estimates derived imply that the dose from inhalation of naturally occurring radon in domestic environments may account for up to 10% of all lung cancers. This risk is especially elevated in heavy cigarette smokers, in whom the lung cancer risk is as much as ten times greater than in nonsmokers (1,2,18).

Factors that Influence Risk

New information from experiments in laboratory animals as well as improved statistical analysis of large epidemological studies has extended our understanding of many of the factors that influence the cancer risk estimation process. Among the most important of these are dose-response relationships, dose rate, age and sex affecting susceptibility to cancer induction, and the temporal distribution of risk.

Dose-Response Relationships. The analysis by the BEIR V Committee (2) and the recent follow-up of the Japanese atomic bomb survivors (5) demonstrate that the dose-effect relationship for cancer mortality other than leukemia shows no significant departure from linearity over the range of doses below 3 Gy. Different neoplasms vary widely in their dose-response relationships, and not all neoplasms are induced by irradiation. The dose-response relationship for leukemia, excluding chronic lymphocytic leukemia, is best described by a linear-quadratic relationship. For certain solid cancers, such as breast and thyroid, the data conform to linearity, while for other organs, e.g., colon, the data are more consistent with a linear-quadratic or quadratic functions. Thus far, it appears that in humans, chronic lymphocytic leukemia, Hodgkin's lymphoma, and certain other lymphomas have not appeared in excess in irradiated populations (2,3).

At present, although data on radiation-induced cancers in human populations and laboratory animals are available over a very wide range of doses, they are not sufficient to define the shape of the dose-response relationship at low doses, for example, below 0.2 Gy. The many epidemiological surveys in support of the dose-incidence models at relatively low doses---childhood leukemia and pelvimetry, thyroid tumors in *tinea capitis* patients, leukemia in atomic bomb survivors, breast cancer in irradiated women, luminous dial painters---all are compatible with a nonthreshold linear dose-response function. The BEIR V Committee concluded that the assessment of the carcinogenic risks from low level radiation must still depend, in large measure, on interpolation from observations at high-dose levels, primarily the Japanese atomic bomb survivors experience, and on assumptions concerning the dose-effect relationships and mechanisms of radiation carcinogenesis (2). The shape of the dose-response relationship at low doses still remains ill-defined and highly uncertain, and the data do not exclude the possible existence of a threshold response for any human neoplasm.

Dose Rate. In laboratory animal experiments and studies of cell transformation *in vitro*, the dose-incidence relationship is strongly dependent on dose and dose rate. For a given neoplasm, the dose-incidence curve generally rises more steeply and is less dependant on on dose rate with high-LET than with low-LET radiation. The carcinogenic effectiveness of low-LET radiation generally

decreases with protraction of dose in the low-dose range, while that of high-LET radiation tends to remain unchanged or even increase in effectiveness (2,3,4,20). The extent to which this reduction in effectiveness obtains for human cancers is not known; comparable human data are fragmentary or lacking. The surveys of breast cancer in irradiated women suggest an excess of breast cancer which is essentially the same magnitude for a given dose, although recent data on the Nova Scotia cohort who received multiple fluoroscopic examinations of the chest do not appear to in accord with this conclusion (2). Efforts to introduce a dose-rate effectiveness factor (DREF) applied to low-LET radiation risk estimates based primarily on the Japanese atomic bomb survivors, in whom the dose was instantaneous and at a high dose rate, have failed. Based on the experimental evidence, the 1977 ICRP Report (21) applied a dose rate reduction factor of about 2.5 for low-dose, low dose-rate exposure; The 1990 ICRP Report (22) recommended that for radiation protection purposes the value of 2 be used, recognizing the choice is somewhat arbitrary and may be conservative. The 1988 UNSCEAR Committee (3) suggested a factor at the lower end of a range of 2 to 10. The National Radiological Protection Board of Great Britain recommended a factor of 3 for all cancers and 2 for breast cancer based on the UNSCEAR conclusions (23). The 1990 BEIR V Committee considered experimental evidence which suggested DREF factors in the range of about 3 to 5 , but chose a conservative factor of 2 or more for application to human cancer risk assessment (2).

High-LET Radiations. Data on human exposure to fission *neutrons* remain fragmentary, and those of internally-deposited *alpha-emitting radionuclides* are complicated by the uncertain dosimetry. In the absence of information on neutron exposure resulting from the reassessment of the Japanese dosimetry, information must be derived from animal experiments. In general, the relative biological effectiveness of high-LET radiation increases with decreasing dose and dose rate, and RBE values as high as 200 has been observed for fission neutrons for certain experimental cancers, but in general range about 10. The RBE for alpha-emitters remains in the range of 20 for bone cancers and lung cancers in humans, and these values are consistent with data derived from laboratory animal experiments (1).

Other Factors. Age at the time of irradiation is a factor in the susceptibility of to radiation-induced cancers and to a number of different types of cancer. For leukemia, the evidence from the Japanese data indicates susceptibility is higher in infancy and childhood than in adolescence and early adult life. Thereafter, susceptibility appears to increase with advancing age. Susceptibility to thyroid cancer appears to be considerably higher in childhood and adolescence than in adult life, decreases with age, and is almost absent after menopause (2). For all other cancers, the data are lacking. Susceptibility to the induction of breast cancer appears only in women and thyroid cancer appears to be higher in females than in males; both are hormone-dependant cancers. For cancers of other sites, *sex* differences are less apparent, but overall relative risks appear to be higher in females. The roles of *ethnic*, *constitutional* and *physiological factors* on susceptibility to radiation carcinogenesis in humans are not well known and as yet cannot be taken into account in estimation of risk. The interaction between radiation and *other carcinogens* in human cancer is, at present, limited to patients treated for cancer with chemotherapy and radiation for Hodgkin's disease and other cancers, to the *tinea capitis* patients exposed to ultraviolet radiation after X-irradiation of the scalp, and to the effects of cigarette smoking and radiation in lung cancer. The interactions of smoking and lung cancer is dependant on the type of radiation exposure; it may be greater than additive in uranium miners and not more than additive in the atomic bomb survivors (1,2). Such interactions are poorly understood and data are insufficient to factor into the risk estimation process.

Temporal Distribution of Risk. Latency and expression of radiation-induced cancers at attained age influence the temporal distribution of cancer risk. The evidence over the past decade has not changed our understanding of latency periods for radiation-induced leukemia or solid cancers. Of importance, however, is the temporal differences in cancer excess between different population surveys. With leukemia and bone cancers, the excess reaches a peak during the first decade and gradually declines thereafter. With solid cancers other than bone, the excess incidence tends to increase with advanced age. In the Japanese atomic bomb survivors, the overall excess cancer mortality has increased with attained age during adult life, generally in parallel with the

baseline incidence; hence, the relative risk during adult life has remained roughly constant with age and time since irradiation, although the relative risk of lung cancer and other cancers has decreased slightly with time during the second and subsequent decades (5). In the ankylosing spondylitis patients, the excess cancer mortality reached a peak during the second decade, after which it appeared to decline, at least for certain sites (7). This latter situation is observed in the radon-exposed underground miners in whom excess lung cancer risk was strongly dependent on age at exposure and time since exposure (1). The basis for these differences in temporal distribution in cancer excess with attained age and time since exposure remains to be determined. The newer methods used to compute the age-specific risks of cancer, namely stratification of the population on age at risk, influence the risk estimates, particularly for overall cancer mortality and for certain age-specific risks of cancer at certain sites (2).

Cancer Risk Estimates

The 1977 UNSCEAR Committee (24) provided the information that served as the basis of the 1977 ICRP risk estimates for carcinogenic effects of radiation (21). Soon thereafter, the 1980 BEIR III Committee found the data to be consistent with these estimates (8). During the past decade, new information has come from a number of epidemiological studies. Because of the influence of numerous factors on the risk estimation process, and the extent to which we fail to understand them, it is not clear how to combine the different data and risk estimates from the different epidemiological studies. Therefore, since the Japanese data provide analysis of the largest population of all ages and both sexes for which quantitative dose-effect data are available, the cancer mortality experience of the Japanese atomic bomb survivors was chosen by the 1988 UNSCEAR Committee (3) and the 1990 BEIR V Committee (2) as the most appropriate basis for projecting risk estimates for the general population.

All Cancers. In the Japanese atomic bomb survivors, the relative risk of cancer mortality, all malignant neoplasms combined, over the follow-up period 1950-1985 has been estimated to be

1.39 per Gy (shielded kerma); this corresponds to an absolute risk of 10.0 excess cancer deaths per 10,000 PYGy; for organ-absorbed dose, these risk estimates are 1.41 and 13.07, respectively (Table 1) (5). These values are influenced by age at exposure and time since exposure. For three broad age groups, viz., the general population, and a working population ages 25 to 64 years, and adults over 25 years, the UNSCEAR estimates indicate the lifetime risk of radiation cancer exposed during adult life, particularly over 65 years, is considerably less than those exposed during childhood and adolescence (Table 3) (3). This influence by age at exposure was found to be consistent and was evident when much narrower 10-year age cohorts were analyzed. The relative risks for many epithelial cancers appear to be slightly higher in females than in males. When combined with the large contribution of breast cancer, this accounts for a considerably higher projected lifetime excess cancer mortality in females (Table 4), some 30-40 percent depending on the risk projection model (3).

Leukemia . Based on the Japanese data (5), the UNSCEAR Report (3) projected an excess cumulative lifetime mortality from leukemia in relation to age at the time of exposure to be about 100 deaths per 10,000 persons at 1 Gy for both the additive and the multiplicative models, and a 40-year plateau period of risk (Table 5). The BEIR V (2) estimate, based on a linear-quadratic dose-effect curve and a modified multiplicative model, was similar. Both in the atomic-bomb survivors and the ankylosing spondylitics, the relative risk of leukemia varies less with age than the absolute risk; the absolute risk is substantially greater in individuals exposed during childhood or late adult life (Table 6). The association between diagnostic irradiation *in utero* and childhood leukemia continues to suggest that the relative risk per unit dose at low doses is considerably higher in late intrauterine life than during any age postnatally. While the relative risk from leukemia appears to be higher in females, higher absolute risks are projected for males.

Cancers Other Than Leukemia.. From the Japanese experience (5), the dose-dependent excess mortality from solid cancers during the 1980-1985 period is estimated to be an excess relative risk of 1.29 at 1 Gy (shielded kerma) and an absolute risk of 7.41 cancer deaths per 10,000 PYGy; the corresponding values for organ-absorbed dose are 1.41 and 10.13, respectively

(Table 1). These values project a cumulative lifetime risk of mortality from all cancers other than leukemia in the range of from about 400 to 1000 per 10,000 persons at 1 Gy, depending on the risk projection model and the age-dependent risk coefficients (Table 3). The risk estimates derived from the Japanese data result primarily from leukemia and cancers of the stomach, lung, female breast and ovary; cancers of other tissues contributed fewer excess cancer deaths (5). The age-specific risk estimates of the 1988 UNSCEAR Committee indicate the cancer excess to be very much larger in those irradiated in childhood than during adult life; the BEIR V Committee narrowed the age cohorts and derived estimates consistent with these findings (Table 7).

When mortality from cancers of other specific sites is assessed, the Japanese data (3,5) provide a total excess risk of 12 cancer deaths per 10,000 PYGy. Based on this and the other epidemiological surveys, the cumulative lifetime excess cancer mortality varies considerably among the different tissues, from a high for lung cancer (59 to 151 per 10,000 persons per Gy) and stomach cancer (86 to 126 per 10,000 persons per Gy) to a low of esophageal cancer (16 to 34 per 10,000 persons per Gy) and multiple myeloma (9 to 22 per 10,000 persons per Gy) (Table 8)(3). Within these ranges, the data suggest that for certain sites, large age differences exist across the whole population. For example, for female breast cancer, susceptibility is highest in women irradiated in childhood and adolescence, decreases with age during adult life, and attains near normal-levels in the postmenopausal years (Table 7).

Alpha Radiations . The 1988 BEIR IV Report (1) examined the radiation risks of radon and other internally-deposited alpha-emitting radionuclides, including polonium, radium, uranium, thorium, and the transuranic elements. The risks of cancer mortality were based exclusively on epidemiological studies, and depended in large measure on the characteristics of the internal emitter and thus the dosimetry, and the circumstances of occupational exposure or medically-associated radiation. The 1990 BEIR V Committee (2) incorporated these risk values in its report, with direct relevance to mortality from cancers of the lung, bone, liver, and leukemia.

The most important target tissues for cancer induction are the respiratory tract, bone, liver and the reticuloendothelial system. Lung cancer risk is derived from the epidemiological surveys of

underground miners who breathe high levels of radon-222 progeny; risk estimates based on dosimetry models of the respiratory tract are complex, and values are based largely on the location of the target cells in the bronchial epithelium, the physiological processes involved in the variable dosimetry, and uncertainties introduced by numerous confounding risk factors, such as smoking. The committee obtained data from four of the principal studies of radon-exposed miners (the Ontario uranium miners, the Saskatchewan uranium miners, the Swedish metal miners, and the Colorado Plateau uranium miners) and developed risk models for lung cancer from its own analyses. In the Committee's model, viz., a modified linear dose-effect relationship, although simple in its mathematical formulation, the excess relative risk after a 5-year lag period varies with time since exposure rather than remaining constant and depends on age at risk; the expression, therefore, is a departure from most previous risk models which have assumed that the relative risk is constant over both age and time. Comparisons of estimates of the lifetime risk of lung cancer mortality due to a lifetime of exposure to radon progeny in terms of WLM and alpha-particle dose to the target cells of the bronchial epithelium --- excess deaths per 10,000 persons exposed --- made by the BEIR and other scientific committees falls within a narrow range of 1.5 to 4.5 per 10,000 person-WLM (1).

The main sources of information on the health effects of radium deposited in the human tissues are the United States cohorts with occupational exposure (mostly dial painters and radium chemists) and medical exposure to radium-226 and radium-228 and the German patients given repeated injections of radium-224, primarily for the treatment of ankylosing spondylitis in adult life and tuberculosis in childhood (1). Malignant effects are almost exclusively the induction of skeletal tumors and carcinomas arising in the paranasal sinuses and mastoid air cells. The evidence for induction of leukemia is weak except at dose levels far in excess of occupational, environmental or therapeutic exposures encountered during the past 50 years. For radium-224 bone tumor induction, the lifetime linear risk is about 200 excess cancers per 10,000 person-Gy, and a minimum latent period of 4 years. For radium-226 and radium-228 bone sarcoma induction, various dose-response functions provide statistically acceptable fits to the data. The cancer risk coefficient is estimated to

be approximately 2 excess cancer deaths per 10,000 PYGy and minimum latent period of 7 years. Carcinomas in the paranasal sinuses and mastoid air cells are observed following exposure to radium-226 or to radium-226 in combination with radium-228, but have not yet been observed among persons exposed to radium-224. The linear risk coefficient is approximately 16 excess cancer deaths per 10,000 PYGy average skeletal dose from radium-226 and a minimum latency period of 10 years.

Risk estimates for thorium-232-induced liver cancer, bone cancer and leukemia have been calculated from the epidemiological surveys of the Thorotrast patients who were injected with collodial thorium-232 dioxide (1). For liver cancer, a lifetime linear risk coefficient is estimated to be about 260 to 300 excess deaths per 10,000 person-Gy (average dose of alpha radiation to the liver), with a 20-year minimum latent period. For bone sarcoma, the lifetime risk coefficient is estimated to be about 55 to 120 excess cancer deaths per 10,000 person-Gy (average dose to the skeleton without bone marrow), and a 5-year minimum latent interval. For leukemia, a lifetime linear risk coefficient of 50 to 60 excess deaths per 10,000 person-Gy is estimated with a 10-year minimum latent interval.

Human exposures to the transuranic elements primarily involve occupationally exposed workers in nuclear facilities. The human data and the alpha-radiation dosimetry are, at present, alone inadequate to provide direct calculation of cancer risk coefficients in the radiosensitive organs and tissues. Currently, human cancer risk estimates may be derived from studies of human populations exposed to other alpha-emitting radionuclides. For lung cancer the lifetime risk estimate is approximately 700 excess deaths per 10,000 person-Gy, based on the estimates for radon-222 and its progeny. For liver cancer, the lifetime risk is approximately 300 excess deaths per 10,000 person-Gy, based on the Thorotrast data (1).

Other Issues

All three committees addressed the importance of cancer incidence data but found it necessary, based on the limited incidence data available for analysis, to rely on mortality data for deriving cancer risk estimates. An exception has been for cancers of the thyroid gland, since the tumors induced by radiation are associated with a relatively low rate of mortality. Numerous populations have been studied, and the risks appear consistent with a linear, nonthreshold function of dose, modified by age, sex, and the type of radiation and dose rate, including external X- and gamma radiations, and the radioiodines. And finally, the total impact of a given cancer death depends on the age of death of the individual; the excess risk in terms of loss of life expectancy per person depends on a number of factors, including the risk protection model. Overall, the loss of life expectancy is estimated to be approximately 1 year at 1 Gy, being greater in those irradiated at younger ages than late in life (2,3).

Some Final Comments

Let us turn now to three important questions that faced the 1990 BEIR V Committee in its deliberations. First, what dose response models should be used, and what are the characteristics of the parameters? Second, how do the application of these models take into consideration dose rate effectiveness factors for low dose-rate exposures? Third, what changes occur in the cancer risk estimates compared with a decade previously, and do these changes, if any, warrant a revision of the risk estimates of the carcinogenic effects of low-dose ionizing radiations?

The BEIR V Committee chose a number of preferred risk models, appropriate for each site, with dose-response relationships derived for leukemia and all other cancers from seven different cohort data sets used for fitting for different cancer sites. For all cancers, including leukemia, the Japanese atomic-bomb survivor data contributed most to the estimation process, whereas the remaining epidemiological studies provided additional information primarily for leukemia, breast

and thyroid. The preferred model for leukemia is a relative risk model with both dose and dose squared terms as well as age at exposure and time since exposure and interaction effects. The preferred model for the Life Span Study data is a relative risk model with a decreasing effect of time since exposure and a declining effect of attained age. A minimum latency of 5 years is assumed. For cancers other than leukemia, the preferred models are relative risk models with a linear dose-response, and age at exposure and time since exposure and interaction effects. In fitting these data, a 10-year latency is assumed. As for leukemia, the effects of time since exposure and of attained age both significantly improved the fit; the relative risk models were more parsimonious or required weaker modifiers.

Since the risk models were derived primarily from data on acute or single high dose-rate exposures, the application of these models to continuous low dose-rate exposures requires consideration of a dose rate effectiveness factor (DREF). The 1990 BEIR V Committee (2) believed that some account should be taken of dose rate effects and suggests a range of DREFs that may be applicable. Such reductions are applied only to the nonleukemia risks, as the leukemia risks already contain an implicit DREF of about 2 owing to the use of the linear-quadratic model. For this reason, the tables of risk estimates in the BEIR V Report (2) record excess risks for leukemia and for all other cancers separately. The 1980 BEIR III Committee (8) chose a DREF of 2.25 from the leukemia data and applied it to the nonleukemia data as a fixed constant. The BEIR V Committee (2) concluded that is could not justify assuming the same dose-response model for all cancer sites, and used separate dose-response models, with no DREF. However, both the 1988 UNSCEAR Committee (3) and the 1990 BEIR V Committee have suggested that the use of a DREF at the lower end if a 2 to 10 range, a DREF if 2 or more, applied to human radiation carcinogenesis, would be reasonable.

The BEIR V Committee (2) estimated lifetime risks for leukemia and for all other cancers resulting from two continuous exposure situations, lifetime and ages 18 to 65 years, and a population-weighted instantaneous exposure to all persons of all ages (Table 9). The results obtained using the committee's preferred modified multiplicative risk models for each site and a life

table analysis accounts for all competing risks including those due to radiation-induced cancer. In general, in the BEIR V Committee (2) estimated that if 100,000 persons received an instantaneous exposure of 0.1 Sv of low-LET radiation, about 790 extra cancer deaths would be expected to occur during their remaining lifetimes in addition to nearly 20,000 cancer deaths that will occur even in the absence of the radiation. Accumulation of the same dose over weeks, months or years, however, is expected to reduce the risk appreciably, possibly by a factor of 2 or more. If that population were exposed continuously to 1 mSv per year for an entire lifetime, about 560 extra cancer deaths would be expected to occur (Table 9).

In the analysis of the follow-up of the atomic bomb survivors, two projection models were examined by the BEIR V Committee. The present data are limited to only 40 years, and those survivors who were irradiated in childhood are yet to attain the age when cancer become prevalent in the general population. It is still not known how the cancer mortality this younger age group will experience in the future will compare with that observed in the populations irradiated at older ages. The most recent data suggest that for all cancers other than leukemia, the excess relative risk varies with age for a given age at exposure than does the absolute risk, indicating the data are more consistent with a multiplicative risk projection model. Because of incomplete follow-up, the projected lifetime risk estimates obtained---either excess absolute or excess relative risks---necessarily differ with time, and the risk projected from the multiplicative model are considerably larger than from the corresponding absolute model. This difference continues to disappear with time as the follow-up of the study populations near completion. Even though the new information has now resulted in higher lifetime risk estimates projected for the general populations, than previously, nevertheless, the risk estimates based on the additive model have increased considerably more than those based on the multiplicative model, and this difference between two projected estimates has decrease in large measure over the past 20 years .

The Committee recognized that the new information and data available since the 1977 ICRP Report (21) resulted in risk estimates that were appreciably higher than previously recorded. Comparison of the risk projections in the 1990 BEIR V Report (2) and the 1980 BEIR III Report

(8) indicated, overall, the risk estimates were now consistently larger. The cancer risk estimates derived with the preferred models used in the BEIR V Report are about 3 times larger for solid cancers (relative risk projection) and about 4 times larger for leukemia than the risk estimates presented in the BEIR III Report (Table 10). There are several reasons for the differences between the two sets of estimates, including the new DS86 atomic-bomb dosimetry applied to the Life Span Study data, the additional years of follow-up, and the changes in the structure of the fitted models. The major differences between the two sets of estimates are for the 1980 BEIR III additive risk models. The 1990 BEIR V Committee concluded that the assumption of a constant additive excess risk is no longer tenable in the light of the data now available, and that the risk estimates from the model provided in the 1980 BEIR III Report were much too low. An evaluation of these risk estimates over the past two decades made by the BEIR and other committees, corrected to be comparable for the excess cumulative lifetime mortality from all cancers attributable to 1 Gy of instantaneous whole-body, low-LET irradiation in 10,000 persons in the general population presents a compelling illustration of these changing events (Table 11) (2). Based on the modified relative risk models for all cancers combined, the current risk estimates are appreciably higher since the BEIR III Report, by factors of about 3 to 4. Accordingly, the Committee can conclude that the new data, and the methods for their analysis, require a reassessment of the previous risk estimates for the carcinogenic effects of low-dose radiation (22).

Epilogue

In concluding my remarks today, I wish to emphasize that my review does not speak for either the BEIR IV or BEIR V Committees or the UNSCEAR Committee or any of its individual members. I speak only for myself. With permission, I have spoken freely about the labors of others, and have quoted extensively from the remarks and conclusions of my scientific colleagues in the committee room; it is their work we recognize. Mr. President, it has been a great personal honor to be invited to address this assembly of scientists of the 32nd Annual Meeting of the Japan

Radiation Research Society, and to describe the experiences of some 5 years of work. I am grateful for this very special privilege, and my wife, Irene, and I thank you, and the scientific and program committees with our deep gratitude, for the opportunity of sharing this remarkable odyssey in science with all of you today.

Acknowledgements

I wish to acknowledge the work of the members of the United States National Academy of Sciences - National Research Council's 1988 BEIR IV and 1990 BEIR V Committees. I had the great privilege of serving with them as a member on both committees, and it has been from their labors, their contributions, their scholarship, their expertise, and their fellowship that I have drawn upon so freely to fashion this review. Mr. Anthony M. Linard provided invaluable assistance in the preparation of the manuscript.

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Table 1

Excess Mortality from Cancer of Various Sites in A-Bomb Survivors, 1950-1985 (from Shimizu et al, 1988)

Site of cancer	Relative risk per Gy	Excess deaths per 10,000 PYGy
Leukemia	6.21	2.94
All except leukemia	1.41	10.13
Esophagus	1.58	0.45
Stomach	1.27	2.42
Large intestine except rectum	1.85	0.81
Lung	1.63	1.68
Female breast	2.19	1.20
Ovary	2.33	0.71
Urinary tract	2.27	0.66
Multiple myeloma	3.29	0.26

Table 2

Relative Risk or Mortality at Ages <85 from Cancers other than Leukemia or Colon in Ankylosing Spondylitis Patients in relation to Time since First Treatment (from Darby et al, 1987)

	Time since First Treatment (y)			
Site	**under 5**	**5.0-24.9**	**over 25**	**Total >5**
Stomach	1.01	1.20	0.62	1.01
Lung	1.22	1.37	0.97	1.21
Breast	1.58	1.88	1.02	1.62
Prostate	3.04	1.24	1.07	1.16
Total				
O/E	76/52.80	385/279.39	1.78/166.56	563/445.95
Ratio	1.44	1.38	1.07	1.26

Table 3

Projections of Lifetime Risk of Fatal Cancer for 10,000 Persons (5,000 Males and 5,000 Females), Instantaneous Exposure to 1 Gy Whole-Body Low-LET Radiation (from UNSCEAR, 1988)

	Risk Projection Model	Excess Fatal Cancers	Years of Life Lost
Total Population	Additive	400-500	9500-12000
	Multiplicative	700-1100	9500-14000
Working Population (aged 25-64)	Additive	400-600	8800-13300
	Multiplicative	700-800	8200-9700
Adult Population (over 25)	Additive	500	8400
	Multiplicative	600	6200

Table 4

Sex Differences in Relative and Absolute Risks of Cancer Mortality in Atomic Bomb Survivors (Shimizu et al, 1988)

	Estimated RR at 1 Gy (shielded kerma)			Excess Deaths per 10,000 PYGy		
Site	**Male**	**Female**	**M/F**	**Male**	**Female**	**M/F**
Leukemia	4.96	4.92	1	3.14	1.8	1.74
All cancers except leukemia	1.17	1.44	0.81	5.76	8.78	0.66

Table 5

Excess Cumulative Lifetime Mortality from Leukemia and Other Cancers after 1 Gy Rapid Whole-Body Low-LET Irradiation, in Relation to Age at the Time of Exposure; A-Bomb Survivor Data (from UNSCEAR, 1988)

Types of Cancer	Additive Risk Projection Model	Multiplicative Risk Projection Model
	(deaths per 10,000 at 1 Gy)	
Leukemia		
adult population	100	86
population of all ages	100	100
Other Cancers		
adult population	360	470
population of all ages	420	1070

Table 6

Relative Risk, Compared with Absolute Risk, of Cancer Deaths in A-Bomb Survivors at 1 Gy (shielded kerma), 1950-1985, in Relation to Age ATB and Age at Death (from Shimizu et al, 1988)

	Age at Time of Death (y)						
Age ATB	**0-19**	**20-29**	**30-39**	**40-49**	**50-59**	**60-69**	**70+**
Leukemia							
All ages	46.47	9.81	4.75	5.68	3.98	1.70	4.40
All Cancers except Leukemia							
All ages	75.32	2.22	1.60	1.58	1.39	1.13	1.29
	(Excess Deaths per 10,000 PYGy)						
Leukemia							
All ages	6.48	2.17	1.16	1.88	1.54	1.09	4.24
All Cancers except Leukemia							
All ages	0.79	0.54	1.98	5.35	9.62	6.85	30.53

Table 7

Cancer Excess Mortality by Age at Exposure and Site for 100,000 Persons of Each Age Exposed to 0.1 Sv (10 rem) (2)

MALES

Age at Exposure	Total	Leukemia	Nonleukemia	Respiratory	Digestive	Other
5	1,276	111	1,165	17	361	787
45	600	108	492	353	22	117
85	110	96	14	17	—	—
Average	770	110	660	190	170	300

FEMALES

Age at Exposure	Total	Leukemia	Nonleukemia	Breast	Respiratory	Digestive	Other
5	1,532	75	1,457	129	48	655	625
45	541	73	468	20	277	71	100
85	90	73	17	—	15	4	—
Average	810	80	730	70	150	290	220

Table 8

Excess Cumulative Lifetime Mortality from Specific Cancers after Acute Exposure to 1 Gy of Organ Absorbed Dose of Low-LET Radiation (from UNSCEAR, 1988)

(Based on the populations of Japan)
(90% C.L. intervals in parentheses)

Malignancy	Multiplicative Risk Projection Model	Additive Risk Projection Model
	(deaths per 10,000 at 1 Gy)	
Red bone marrow	97	93
All cancers except leukemia	610	360
Bladder	39	23
Breast	60	43
Colon	79	29
Lung	151	59
Multiple myeloma	22	9
Ovary	31	26
Esophagus	34	16
Stomach	126	86
Remainder	114 118	103 66
Total	707	453

Table 9

Excess Cancer Mortality Estimates and their Statistical Uncertainty - Lifetime Risks per 100,000 Exposed Persons (2)

	Male			Female		
	Total	Nonleukemia	Leukemia	Total	Nonleukemia	Leukemia
Single exposure to 0.1 Sv (10 rem)	770	660	110	810	730	80
90% confidence limits	540–1,240	420–1,040	50–280	630–1,160	550–1,020	30–190
Normal expectation	20,510	19,750	760	16,150	15,540	610
Continuous lifetime exposure to 1 mSv/y (0.1 rem/y)	520	450	70	600	540	60
90% confidence limits[d]	410–980	320–830	20–260	500–930	430–800	20–200
Normal expectation	20,560	19,760	790	17,520	16,850	660
Continuous exposure[e] to 0.01 Sv/y (1 rem/y) from age 18 until age 65	2,880	2,480	400	3,070	2,760	310
90% confidence limits	2,150–5,460	1,670–4,560	130–1,160	2,510–4,580	2,120–4,190	110–910
Normal expectation	20,910	20,140	780	17,710	17,050	650

Table 10

Comparison of Lifetime Cancer Mortality Risk Estimates 100,000 Persons Instantaneous Exposure to 0.1 Sv* (2,8)**

		Model	Males	Females
Leukemia	BEIR III	(LQ, AR)***	27.4	18.6
	BEIR V	(LQ, RR)***	110	80
	BEIR V/BEIR III		**4.0**	**4.3**
Nonleukemia	BEIR III	(L, RR)	192	213
	BEIR V	(L, RR)	660	730
	BEIR V/BEIR III		**3.4**	**3.4**

* DREF of 2 or more not included

** Modified from Table 1, Jablon, 1990 (27)

*** LQ = Linear Quadratic, L = Linear, AR = Absolute Risk, RR = Relative Risk

Table 11

Projected Excess Cumulative Lifetime Mortality from Cancer, All Types Combined, Attributable to 1 Gy Acute Whole-Body Low-LET Irradiation of the General Population

Source of Estimate	D/R Model	Additive Risk Projection Model	Multiplicative Risk Projection Model
		(deaths per 10,000 persons) *	
BEIR I, 1972 (25)	L	120	620
UNSCEAR, 1977 (21)	L	200	--
BEIR III, 1980 (8)	L	80-180**	230-500**
NUREG, 1985 (26)	LQ	290	520
UNSCEAR, 1988 (3)	L	400*-500**	700**-1100*
BEIR V, 1990 (2)	L	--	**790**

* age-specific risk coefficients
** age-averaged risk coefficient

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