Attachment 2

Executive Summary, Discussion and Conclusions from NCRP Report No. 136 "Evaluation of the Linear-Nonthreshold Dose-Response Model for Ionizing Radiation"

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NCRP Report No. 136

Evaluation of the Linear-Nonthreshold Dose-Response Model for Ionizing Radiation

Recommendations of the
NATIONAL COUNCIL ON RADIATION
PROTECTION AND MEASUREMENTS

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[For detailed information on the availability of NCRP publications see page 273.]

Preface

In developing its basic radiation protection recommendations, as given in NCRP Report No. 116, *Limitation of Exposure to Ionizing Radiation* (NCRP, 1993a), the Council reiterated its acceptance of the linear-nonthreshold hypothesis for the risk-dose relationship. Specifically, "based on the hypothesis that genetic effects and some cancers may result from damage to a single cell, the Council assumes that, for radiation-protection purposes, the risk of stochastic effects is proportional to dose without threshold, throughout the range of dose and dose rates of importance in routine radiation protection. Furthermore, the probability of response (risk) is assumed, for radiation protection purposes, to accumulate linearly with dose. At higher doses received acutely, such as in accidents, more complex (nonlinear) dose-risk relationships may apply." This Report is the result of an in-depth review by NCRP Scientific Committee 1-6 of the scientific basis for this assumption, *i.e.*, the relationship between dose and risk at low doses.

Scientific Committee 1-6 sought and obtained written and oral input from several scientists in the United States who held many different views regarding the science associated with this subject and I want to thank those scientists for their frank and candid input to the Committee's work.

Since this Committee was constituted to address the scientific issues, the implications of the Committee's work for radiation protection policy will be addressed by NCRP at a later point in time.

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Charles B. Meinhold
President

1. Executive Summary

This Report presents an evaluation of the existing data on the dose-response relationships and current understanding of the health effects of low doses of ionizing radiation.[1] This reevaluation was carried out by Scientific Committee 1-6 of the National Council on Radiation Protection and Measurements (NCRP), which was charged to reassess the weight of scientific evidence for and against the linear-nonthreshold dose-response model, without reference to associated policy implications. The evaluation was prompted by the need to reassess the common use, for radiation protection purposes, of the linear-nonthreshold dose-response hypothesis in the light of new experimental and epidemiological findings, including growing evidence of adaptive responses to small doses of radiation which may enhance the capacity of cells to withstand the effects of further radiation exposure, and new evidence concerning the possible nature of neoplastic initiation.

The evaluation focuses on the mutagenic, clastogenic (chromosome-damaging), and carcinogenic effects of radiation, since these effects are generally postulated to be stochastic and to increase in frequency as linear-nonthreshold functions of radiation dose.[2] For each type of effect, the relevant theoretical, experimental and epidemiological data are considered. Furthermore, in an effort to avoid overlooking pertinent data in the evaluation, input was obtained from authorities in the field and from the scientific community at large.

The evaluation begins by considering the way in which radiation energy is deposited within cells and its implications for dose-response relationships. As is customary, the amount of radiation producing an effect is conveniently specified as the energy absorbed per unit mass in the irradiated system; *i.e.*, the dose (D). At the outset, it is noted that virtually all existing experimental and epidemiological data on the effects of sparsely ionizing [*i.e.*, low linear-energy transfer (LET)] radiation come from observations at doses far above those in

[1] In this Report, the word "dose" is frequently used in its generic sense.

[2] Publication 26 of the ICRP (1977) was the first to describe in detail that "stochastic" effects are those for which the probability of an effect occurring, rather than its severity, is regarded as a function of dose without a threshold.

which a single cell is struck, on the average, by no more than one radiation track. This means that any effects attributable to lower doses of radiation in the millisievert range can be estimated only by extrapolation, guided by radiation damage and repair models. Based on direct experimental observations involving alpha-particle microbeam experiments and theoretical considerations, it is concluded that cellular traversal by a single radiation track of any type of ionizing radiation has a non-zero probability of depositing enough energy in a critical macromolecular target, such as deoxyribonucleic acid (DNA), to injure, but not necessarily kill the cell in question. Hence, when the average number of traversals is well below one, it is concluded that the number of independently affected cells may increase as a nonthreshold function of the dose. Moreover, there is now evidence that cells in the neighborhood of those hit may also exhibit signs of radiation damage. The dose-response relationships have not been determined, but if each hit cell influences a number of surrounding cells, there could be a linear dose response until all cells are hit (Azzam *et al.*, 1998; Deshpande *et al.*, 1996; Lehnert and Goodwin, 1997; Lorimore *et al.*, 1998; Mothersill and Seymour, 1997; 1998; Nagasawa and Little, 1992).

Of the various macromolecular targets within cells that may be altered by radiation, DNA is the most critical, since genomic damage may leave a cell viable, but permanently altered. Several types of initial or primary DNA damage are known to result from ionizing irradiation, including single-strand breaks (ssbs), nucleotide base damages (bds) and loss, DNA-protein cross-links (dpcs), double-strand breaks (dsbs), and multiply-damaged sites (mds) of a type which is extremely rare in nonirradiated cells. Most such lesions in DNA are repairable to varying degrees, depending on the repair capacity of the affected cells. Dsbs and mds are induced only by ionizing radiation (and some radiomimetic chemicals) and are complex and extremely difficult substrates for DNA repair enzymes to handle; the repair of these lesions has been observed to be inaccurate where their frequencies have been amenable to measurement. Although the extent to which repair may alter their production at doses in the millisievert range remains to be determined, it is noteworthy that at higher doses all types of DNA lesions appear to be formed linearly with increasing dose and that they are induced so sparsely in the low-dose range that interactions between adjacent lesions produced by different radiation tracks are extremely rare.

Any DNA lesions that remain unrepaired, or are misrepaired, may be expressed as point mutations (resulting from nucleotide base-pair substitutions or from the insertion or deletion of small numbers of base pairs), larger deletions (involving the loss of hundreds-to-millions of base pairs), genetic recombination events (involving the exchange of sequences of base pairs between homologous chromosomes), and chromosome aberrations. Mutations of all types appear to be inducible by ionizing radiation, but their dose-response curves vary in shape, depending on the dose, the type of mutation scored, the LET and dose rate of the radiation, and the genetic background of the exposed cells. The frequency of mutations induced by a given dose of low-LET radiation has generally been observed to decrease with decreasing dose rate, implying that some premutational damage that does not accumulate too rapidly in the exposed cells can be repaired. The capacity for repair of premutational damage is also evident from the fact that prior exposure to a small "conditioning" dose of low-LET radiation may reduce the frequency with which mutations are produced by a subsequent "challenge" dose in cells of some individuals. It is noteworthy, nevertheless, that mutational changes of various types (including those types implicated in carcinogenesis) have generally been observed to be induced with linear kinetics at low-to-intermediate dose levels in human and animal cells.

The misrepair of lesions in DNA can also give rise to chromosome aberrations, the frequency of which varies markedly with the dose, dose rate, and LET of the radiation. In cells exposed to high-LET radiation, the response typically rises as a linear function of the dose, with a slope that is essentially dose-rate-independent, whereas in cells exposed to low-LET radiation the curve rises less steeply, as a linear-quadratic function of the dose after acute irradiation. At low-dose rates, the linear portion of the curve predominates and is a limiting slope at low doses. The apparent linearity of the latter dose-response relationship implies that traversal of the cell by a single low-LET radiation track may occasionally suffice to cause a nonlethal chromosome aberration, but the likelihood of such an effect would depend on the fidelity with which DNA damage is repaired at such low-dose levels.

It is noteworthy that prior exposure to a small (*e.g.*, 10 mSv) "conditioning" dose of radiation has been observed to enhance the repair of chromosome aberrations for such DNA lesions in the cells of some persons; however, the existing data imply that this type of adaptive response is not elicited in every individual, that the response lasts no more than a few hours when it does occur, that a dose of at least 5 mSv delivered at a dose rate of at least 50 mSv min^{-1} is required to elicit the response, and that the response typically reduces the aberration frequency by no more than one-half. On the basis of the existing evidence it appears likely that this adaptive response acts primarily to reduce the quadratic (two-hit) component

of the dose-response curve, without changing the slope of the linear component. While the existing data do not exclude the possibility that a threshold for the induction of chromosome aberrations may exist in the millisievert dose range, there is no body of data supporting such a possibility, nor would such a threshold be consistent with current understanding of the mechanisms of chromosome aberration formation at low doses.

The significance of nonlethal mutations and chromosome aberrations is that they are implicated in the causation of cancer, a clonal disorder that may result from such changes in only one cell in the relevant organ. The types of functional genetic changes implicated thus far in carcinogenesis include the activation of oncogenes, the inactivation or loss of tumor-suppressor genes, and alterations of various other growth-regulatory genetic elements (*e.g.*, loss of apoptosis genes, mutation in DNA repair genes). The specific roles that such changes may play in the cancer process remain to be fully elucidated. However, the neoplastic transformation of cells by irradiation *in vitro*, a process which is analogous in many respects to carcinogenesis *in vivo*, typically involves a step-wise series of such genetic alterations, in the course of which the affected cells often accumulate progressively, growing numbers of mutations and/or chromosomal abnormalities, a pattern indicative of genomic instability. Although the precise nature of each step in the process remains to be elucidated in full, the frequency with which initial *in vitro* alterations are produced by ionizing radiation typically exceeds any known *in vivo* radiation-induced mutation rate by several orders of magnitude, suggesting that epigenetic changes, as well as genetic changes, are involved. Further research into the significance of *in vitro* neoplastic transformation for *in vivo* carcinogenesis is clearly needed. It is also noteworthy that susceptibility to neoplastic transformation *in vitro* varies markedly with the genetic background of the exposed cells, their stage in the cell cycle, the species and strain from which the cells were derived, and many other variables. The process is further complicated by evidence that transformed cells may release diffusible substances into the surrounding medium that enhance the transformation of neighboring cells. Not surprisingly, therefore, the dose-response curve for neoplastic transformation is complex in shape and subject to variation, depending on the particular cells and experimental conditions under investigation. Little is presently known about the shape of the curve in the low-dose domain, but evidence suggests that a small percentage of exposed cells may be transformed by only one alpha-particle traversal of the nucleus.

The dose-response relationships for carcinogenic effects of radiation have been studied most extensively in laboratory animals, in

which benign and malignant neoplasms of many types have been observed to be readily inducible by large doses of radiation. The dose-response curves for such neoplasms vary widely, depending on the neoplasm in question, the genetic background, age and sex of the exposed animals, the LET and dose rate of irradiation, and other variables. In general, low-LET radiation is appreciably less tumorigenic than high-LET radiation, and its tumorigenic effectiveness is reduced at low-dose rates, whereas the tumorigenic effectiveness of high-LET radiation tends to remain relatively constant. Not every type of neoplasm is inducible, however; some types actually decrease in frequency with increasing dose, and there are others that are induced in detectable numbers only at high-dose levels, signifying the existence of effective or actual thresholds for their induction. For certain types of neoplasms, however, and for the life-shortening effects of all radiation-induced neoplasms combined, the data are consistent with (linear or linear-quadratic) nonthreshold relationships, although the data do not suffice to define the dose-response relationships unambiguously in the dose range below 0.5 Sv. The variations among neoplasms in dose-response relationships point to differences in causal mechanisms which remain to be elucidated. Nevertheless, it is clear from the existing data that tumor induction *in vivo* is a multistage process in which the initial radiation-induced alteration typically occurs at a frequency exceeding that of any known radiation-induced specific locus mutation and is followed by the activation of oncogenes, inactivation or loss of tumor-suppressor genes, and other mutations and/or chromosomal abnormalities, often associated with genomic instability in the affected cells.

Dose-dependent increases in the frequency of many, but not all, types of neoplasms are well documented in human populations as well as in laboratory animals. The dose-response relationships for such neoplasms likewise vary, depending on the type of neoplasm, the LET and dose rate of irradiation, the age, sex, and genetic background of the exposed individuals, and other variables. The data come largely from observations at relatively high doses and dose rates and do not suffice to define the shape of the dose-response curve in the millisievert dose range; however, it is noteworthy that: (1) the dose-response curve for the overall frequency of solid cancers in the atomic-bomb survivors is not inconsistent with a linear function down to a dose of 50 mSv; (2) there is evidence suggesting that prenatal exposure to a dose of only about 10 mSv of x ray may suffice to increase the subsequent risk of childhood cancer; (3) analysis of the pooled data from several large cohorts of radiation workers supports the existence of a dose-dependent excess of leukemia from occupational irradiation that is similar in magnitude to the excess

observed in atomic-bomb survivors; (4) a dose of about 100 mSv to the thyroid gland in childhood significantly increases the incidence of thyroid cancer later in life; and (5) highly fractionated doses of about 10 mSv per fraction, delivered in multiple fluoroscopic examinations during the treatment of pulmonary tuberculosis (TB) with artificial pneumothorax, appear to be fully additive in their carcinogenic effects on the female breast in women exposed under the age of 50, although much less than fully additive in carcinogenic effects on the lung. At the same time, it is important to note that the rates of cancer in most populations exposed to low-level radiation have not been found to be detectably increased, and that in most cases the rates have appeared to be decreased. For example, the large pooled study of radiation worker cohorts did not show positive effect for solid tumors. In general, however, because of limitations in statistical power and the potential for confounding, low-dose epidemiological studies are of limited value in assessing dose-response relationships and have produced results with sufficiently wide confidence limits to be consistent with an increased effect, a decreased effect, or no effect.

Another factor complicating the assessment of the dose-response relationship is uncertainty about the extent to which the effects of radiation may be reduced by adaptive responses in the low-dose domain. Adaptive responses may account, at least in part, for the reduced effectiveness of low-LET radiation at low-dose rates. It is not clear, however, that such responses can be elicited by a dose of less than 1 mSv delivered at a rate of less than 0.05 Sv min^{-1}, or that the responses can increase the fidelity of DNA repair processes sufficiently to make the processes error-free. In a significant percentage of individuals, moreover, the capacity to elicit such responses appears to be lacking. The available data on adaptive responses do not suffice, therefore, to either exclude or confirm a linear-nonthreshold dose-incidence relationship for mutagenic and carcinogenic effects of radiation in the low-dose domain.

In conclusion, the weight of evidence, both experimental and theoretical, suggests that for many of the biological lesions which are precursors to cancer (such as mutations and chromosome aberrations) the possibility of a linear-nonthreshold dose-response relationship at low radiation doses cannot be excluded. The weight of epidemiological evidence, of necessity somewhat more limited, also suggests that for some types of cancer there may be no significant departure from a linear-nonthreshold relationship at low-to-intermediate doses above the dose level where statistically significant increases above background levels of radiation can be detected. The existing epidemiological data on the effects of low-level irradiation

are inconclusive, however, and, in some cases, contradictory, which has prompted some observers to dispute the validity of the linear-nonthreshold dose-response model for extrapolation below the range of observations to zero dose. Although other dose-response relationships for the mutagenic and carcinogenic effects of low-level radiation cannot be excluded, no alternate dose-response relationship appears to be more plausible than the linear-nonthreshold model on the basis of present scientific knowledge.

In keeping with previous reviews by the NCRP (1980; 1993b; 1997), the Council concludes that there is no conclusive evidence on which to reject the assumption of a linear-nonthreshold dose-response relationship for many of the risks attributable to low-level ionizing radiation although additional data are needed (NCRP, 1993c). However, while many, but not all, scientific data support this assumption (NCRP, 1995), the probability of effects at very low doses such as are received from natural background (NCRP, 1987) is so small that it may never be possible to prove or disprove the validity of the linear-nonthreshold assumption.

12. Discussion and Conclusions

The extent to which the existing data on the mutagenic, clastogenic and carcinogenic effects of ionizing radiation are, or are not, compatible with the linear-nonthreshold dose-response hypothesis has been evaluated in the foregoing sections of the Report, taking into account the relevant experimental and epidemiological evidence. The conclusions that may be drawn from the evaluation are necessarily limited by the dearth of quantitative information on dose-response relationships in the low-dose domain, incomplete knowledge of the mechanisms of the effects in question, and uncertainty about the degree to which induction of the effects may be inhibited by adaptive reactions under conditions of low-level irradiation. These limitations notwithstanding, the conclusions that emerge and the rationale underlying them are summarized in the following.

At the outset, it must be noted that radiation imparts its energy to living matter through a stochastic process, such that a single ionizing track has a finite probability of depositing enough energy in traversing a cell to damage a critical molecular target within the cell, such as DNA. Furthermore, the amount of the various types of DNA damage that are known to result from irradiation appears to increase linearly with the dose in the low-to-intermediate dose range. Also, although most such DNA damage is reparable to varying degrees, some types of lesions—namely, dsbs and mds—are often repaired through a process that is error-prone. Because of the vast number of target cells, vanishingly small frequencies of nonlethal, unrepaired or misrepaired lesions may nevertheless result in a finite number of cells undergoing a cancer-initiating event even at low doses, although the possibility of a threshold in the millisievert range cannot be excluded.

Those lesions in DNA that remain unrepaired or are misrepaired may be expressed initially in the form of mutations, the frequency of which increases with the dose of radiation over the dose range in which the effects are amenable to measurement. Although the shape of the dose-response curve varies, depending on the LET of the radiation, the dose rate, the type of mutation, and other variables, it is noteworthy that mutations of types implicated in carcinogenesis—namely, point mutations and partial deletion mutations—have been

observed to be inducible at relatively low doses (*e.g.*, <0.01 Gy) with apparently linear-nonthreshold dose-response relationships in various kinds of cells.

Damage to DNA can also give rise to chromosomal alternations, which, in turn, may be linked to the causation of various cancers. Most chromosomal structural changes result from the misrepair of DNA lesions (dsbs, base alterations, cross-links, or more complex lesions) that arise close together in space and time. The frequency of such aberrations therefore typically increases as a linear function of the dose of high-LET radiation. With low-LET radiation, the frequency increases as a linear-quadratic function of the dose in cells exposed acutely, but as the dose rate is reduced, the quadratic component of the response decreases progressively, leaving a response that appears linear in cells exposed chronically. Thus the data imply that traversal of the cell nucleus by a single low-LET radiation track may occasionally suffice to cause a chromosomal aberration. Data from human population monitoring are consistent with this conclusion. At doses in the millisievert range, however, the shape of the dose-response curve is open to question, owing to uncertainty about the fidelity of repair in the low-dose domain and a threshold cannot be excluded.

Cells irradiated in culture have also been observed to undergo dose-dependent neoplastic transformation. The process of transformation appears to involve a succession of steps, during which the affected cells characteristically accumulate a growing number of mutations and/or chromosomal abnormalities, indicating the presence of genomic instability. Although the details of each step remain to be elucidated in full, the activation of oncogenes and/or inactivation or loss of tumor-suppressor genes have been implicated in some instances. Epigenetic changes are also suggested, in view of the fact that the radiation-induced alteration occurs with a frequency that is orders of magnitude above any known mutation rates. Furthermore, susceptibility to transformation varies markedly with the genetic background of the exposed cells and other variables. Not unexpectedly, therefore, the dose-response curve for transformation is complex in shape and subject to variation, depending on the particular experimental conditions investigated. Few data are available as yet on the shape of the curve at low doses, but there is evidence that exposure to a dose involving only one alpha particle traversal per nucleus may suffice to transform a small percentage of exposed cells. The microbeam data, discussed earlier, show that exactly one particle per nucleus is less effective at producing transformation than an average of one with a Poisson distribution. This implies that the cells transformed are those receiving multiple traversals. In the

case of low-LET radiations the lowest dose at which a statistically significant increase of transformation over background has been demonstrated is 10 mGy.

In laboratory animals, benign and malignant neoplasms of many types are readily inducible by irradiation. The dose-response curves for such neoplasms vary markedly, depending on the neoplasm in question, the species, strain, sex, and age of the exposed animals, the LET and the dose rate of the radiation, and other variables. In general, the tumorigenic effectiveness of low-LET radiation is appreciably lower than that of high-LET radiation and is reduced at low doses and low-dose rates, whereas the tumorigenic effectiveness of high-LET radiation tends to remain constant or even to increase in some instances with protraction. The available information does not suffice to define the dose-response curve unambiguously for any neoplasm in the dose range below 0.5 Sv, and it indicates the existence of substantial thresholds for the induction of some types of neoplasms. For other types of neoplasms, however, and for the overall life-shortening effects of all radiation-induced neoplasms combined, the data are not inconsistent with a linear-nonthreshold relationship in mice exposed chronically to low-to-intermediate doses of low-LET radiation. The basis for the differences among neoplasms in dose-response relationships remains to be determined. Although the data imply that the initial cellular alteration induced by irradiation *in vivo* typically occurs far more frequently than a mutation at any one genetic locus and that it tends to be followed ultimately by genomic instability in the affected cells, the precise nature and sequence of each of the steps that may be involved in the induction of a particular neoplasm are yet to be fully characterized. Noteworthy, nevertheless, is the fact that various cancer-susceptibility genes, hormones, and other growth-regulating factors have been implicated in a growing number of instances.

Dose-dependent increases in the frequency of many types of benign and malignant neoplasms are also well documented in irradiated human populations. Likewise, it is evident from the available data that the dose-response relationship for such neoplasms may vary, depending on the type of neoplasm, the LET and dose rate of the radiation, the age, sex, and genetic background of the exposed individuals, and other factors. For the most part, moreover, the data come from observations at relatively high doses and dose rates, and they do not suffice to define the shape of the dose-response curve in the low-dose domain. Nevertheless, the following points are noteworthy: (1) in the Japanese atomic-bomb survivors, although the dose-response curve for leukemia appears to be mainly linear-quadratic, the dose-response curve for the overall frequency of solid cancers is not inconsistent with a linear-nonthreshold relationship down to a dose of 50 mSv; (2) prenatal exposure to a dose of only about 10 mGy of x rays appears to increase the risk of cancer in the exposed fetus; (3) analysis of the pooled data from several large cohorts of radiation workers discloses a dose-dependent excess of leukemia (but not solid cancers) in this population that is similar in magnitude to the excess observed in atomic-bomb survivors; (4) a dose of about 100 mSv to the thyroid gland in childhood causes a substantial increase in the risk of thyroid cancer later in life; (5) highly fractionated doses of about 10 mGy per fraction, delivered in multiple fluoroscopic examinations during the treatment of pulmonary TB with artificial pneumothorax, appear to be fully additive in their carcinogenic effects on the female breast, although much less than fully additive in carcinogenic effects on the lung; and (6) certain rare hereditary traits appear to increase sensitivity to radiation-induced cancer, although, there are as yet insufficient data to determine whether the more common hereditary cancer-related gene mutations (*e.g.*, *FAP*, *HNPCC*, *BRCA1*, *BRCA2*, and *ATM* genes) do so. However, some evidence from large low-dose studies has been negative, *e.g.*, there was no dose-response relationship for solid tumors in the large pooled study of workers exposed to radiation (Cardis *et al.*, 1995).

Assessment of the dose-response relationships for low-level irradiation is also complicated by uncertainty about the extent to which adaptive reactions may reduce the effects of radiation in the low-dose domain. Although adaptive reactions may well account in part for dose-dependent and dose-rate-dependent variations in the effectiveness of low-LET radiation at higher doses and higher dose rates, they have yet to be shown to be elicitable in cells or organisms exposed to less than 10 mGy delivered at a dose rate of less than 50 mGy min^{-1}. Furthermore, cells from different individuals vary markedly in their ability to mount such reactions. Given the various lines of evidence that are consistent with the linear-nonthreshold dose-response hypothesis, the existing data on adaptive reactions provide no convincing evidence to the contrary.

In conclusion, although the evidence for linearity is stronger with high-LET radiation than with low-LET radiation, the weight of the evidence, both experimental and theoretical, suggests that the dose-response relationships for many of the biological alterations that are likely precursors to cancer are compatible with linear-nonthreshold functions. The epidemiological evidence, likewise, while necessarily limited to higher doses, suggests that the dose-response relationships for some, but not all, types of cancer may not depart significantly from linear-nonthreshold functions. The existing data do not exclude other dose-response relationships. Further efforts to clarify the relevant dose-response relationships in the low-dose domain are strongly warranted.