Comments

of the

Natural Resources Defense Council

& Committee to Bridge the Gap

on the

Nuclear Regulatory Commission's

Notice of Docketing Petitions for Rulemaking

10 CFR Part 20

Linear No-Threshold Model and Standards of Protection Against Radiation

Docket ID No. NRC-2015-0057

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On June 23, 2015, the Nuclear Regulatory Commission had published in the Federal Register a notice of docketing and request for comment on three petitions for rulemaking requesting NRC amend its "Standards for Protection Against Radiation" regulations and change the basis of those regulations from the Linear No-Threshold (LNT) model of radiation protection to the radiation hormesis model. 80 Fed. Reg. 35879 (June 23, 2015).

As NRC explained, the radiation hormesis model provides that exposure of the human body to low levels of ionizing radiation is beneficial and protects the human body against deleterious effects of high levels of radiation. By contrast, the LNT model, the longtime and current basis for radiation protection standards across federal agencies and indeed, worldwide, provides that radiation is always considered harmful, there is no safety threshold, and biological damage caused by ionizing radiation (essentially the cancer risk) is directly proportional to the amount of radiation exposure to the human body (response linearity). The petitions were docketed by the NRC in the winter and spring of this year and have been assigned Docket Numbers PRM-20-28, PRM-20-29, and PRM-20-30, respectively. These petitions urge amendment to NRC's Standards for Protection Against Radiation (10 C.F.R. §20). The Natural Resources Defense Council, Inc. (NRDC) and Committee to Bridge the Gap (CBG) submit the following technical and jurisdictional comments in opposition to these petitions.

Technical Comment on the Petitions

As an initial matter, we concur with the U.S. Environmental Protection Agency's (EPA) comments on the LNT model sent by EPA in response to the proposed petition for rulemaking. *See* Attachment 1, *U.S. Environmental Protection Agency's Comments on Linear No-Threshold Model and Standards for Protection against Radiation; Notice of Docketing and Request for Comment ID: NRC-215-0057-0010,* Letter from Jonathan D. Edwards, Director, EPA Radiation Protection Division, October 7, 2015 (hereinafter "Att. 1").

As EPA notes, "the …Carcinogen Assessment Guidelines specify that LNT should be used as a default assumption unless there is compelling evidence that the biological mechanism for carcinogenesis is inconsistent with LNT." Att. 1 at 4 of pdf. There is no such compelling evidence and the available (and extensive) epidemiological data are broadly consistent with a linear dose-response for radiation cancer risk at moderate and low doses.

In addition to the EPA, several international and US scientific groups including the National Academy of Sciences (Biological Effects of Ionizing Radiation VII (BEIR VII),[1] US National

[1] *See Health Risks from Exposure to Low Levels of Ionizing Radiation, BEIR VII Phase 2 (2006),* Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation; Board on Radiation Effects Research; Division on Earth and Life Studies; National Research Council, published 2006. The BEIR VII report states in pertinent part at 6, "[t]he committee judged that the linear no-threshold model (LNT) provided the most reasonable description of the relation between low-dose exposure to ionizing radiation and the incidence of solid cancers that are induced by ionizing radiation." Found online at http://www.nap.edu/catalog/11340/health-risks-from-exposure-to-low-levels-of-ionizing-radiation.

Council on Radiation Protection and Measurements (NCRP),[2] and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) [3] evaluated the effects of low doses of radiation. Low doses are defined in these studies as those ranging from nearly zero to about 100 millisivert (mSv.) Their studies showed that even low doses of ionizing radiation are likely to pose some risk of adverse health effects and there is no safe or threshold dose of radiation below which low levels of radiation can be demonstrated to be harmless or beneficial. As EPA noted in its short commentary on the petitions, "[o]ver the last half century, numerous authoritative national and international bodies have convened committees of experts to examine the issue of LNT as a tool for radiation regulation and risk assessment … Again and again, these bodies have endorsed LNT as a reasonable approach to regulating exposures to low dose radiation." Att. 1 at 4 of pdf.

It is the clear conclusion of the EPA, the National Academies, NRDC and CBG that the LNT model is scientifically sound and must remain as the basis for regulating exposures to ionizing radiation. There is no technical basis to entertain these petitions beyond their initial compliance with the submission requirements of 10 C.F.R. §2.802.

Jurisdictional Comment on the Petitions

The act of moving forward with a rulemaking without the complete, early and initial engagement of the EPA – an unlikely occurrence given EPA's comments on the petitions (*see* Att. 1) – would contravene long established law and would pose potential unnecessary and ill-advised mischief to the regulatory scheme for the protection of workers and the public from ionizing radiation.

As NRC is well aware,

> In forming EPA, the authors of Reorganization Plan No. 3 created a new national approach for protecting the general public from the harmful exposure to radiation. Two key radiation protection functions would now be housed in a single agency – the promulgation of generally applicable environmental standards to limit man-made radioactive materials in the environment, and the development of national radiation protection guidance for Federal and State agencies to follow in the development of their radiation protection programs and regulations. Along with

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[2] *See* Att. 2, NCRP Report No. 136, *Evaluation of the Linear Nonthreshold Dose-Response Model for Ionizing Radiation* (at 7) where the NCRP states "[t]he 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."

[3] *See* UNSCEAR 2000 report ANNEX G, *Biological effects at low radiation doses* (at 86) where the report states "[t]he increase in the frequency of these aberrations at such an extremely low dose rate suggested that there is no threshold dose for the induction of chromosome aberrations." Found online http://www.unscear.org/docs/reports/annexg.pdf.

> these responsibilities, EPA was provided extensive research and surveillance capabilities to support the development of national guidance and standards, as well as the authority to provide technical assistance to the States.

See Radiation Protection at EPA, The First 30 Years, United States Environmental Protection Agency, Office of Radiation and Indoor Air, EPA 402-B-00-001, August 2000.[4]

Further, essential radiation standard setting functions of the Atomic Energy Commission, administered through its Division of Radiation Protection Standards, were transferred to EPA "to the extent that such functions consist of establishing generally applicable environmental standards for the protection of the general environment from radioactive material." *Id.* at 4, 5. Under the authority of the Atomic Energy Act, these standards were defined as "limits on radiation exposures or levels, or concentrations or quantities of radioactive material, in the general environment outside the boundaries of locations under the control of persons possessing or using radioactive material."

NRC itself sets standards for protection against ionizing radiation resulting from activities conducted under the licenses it issues. *See* 10 C.F.R. § 20.1001(a). It is the express purpose of NRC's regulations to ensure that the "total dose to an individual (including doses resulting from licensed and unlicensed radioactive material and from radiation sources other than background radiation) does not exceed the standards for protection against radiation prescribed in the regulations in this part." 10 C.F.R. § 20.1001(b). Whether those current standards are adequately protective or vigorously enforced is not the subject of this response to these petitions.

Overlapping with NRC standards and in controlling fashion (as noted above, the promulgation of generally applicable environmental standards to limit man-made radioactive materials in the environment, and the development of national radiation protection guidance for Federal and State agencies to follow in the development of their radiation protection programs and regulations are housed at EPA), EPA sets standards for "radiation doses received by members of the public in the general environment and to radioactive materials introduced into the general environment as the result of operations which are part of a nuclear fuel cycle." 40 C.F.R. § 190.01. NRC's regulatory structures are supposed to be consistent with those set by EPA. Indeed, NRC rules, when addressing dose limits for individual members of the public, state that "[i]n addition to the requirements of this part, a licensee subject to the provisions of EPA's generally applicable environmental radiation standards in 40 CFR part 190 shall comply with those standards. § 20.1301(e). In either case, EPA's and NRC's radiation protection standards adhere to the LNT model and have done so for decades.

To abandon the LNT model – as the petitioners suggest – would expressly contravene EPA's standards and put (if for some unknown reason adopted after final rulemaking that would surely be subject to challenge) the NRC's weakened, scientifically debased regulatory scheme in opposition to EPA, the National Academies, and the vast majority of analytical literature on the subject of ionizing radiation.

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[4] Found online at http://www2.epa.gov/sites/production/files/2015-05/documents/402-b-00-001.pdf.

In conclusion, there are no technical or regulatory reasons identified in these petitions that would justify lowering radiation protections for workers and the public in general or departing from the adherence to the LNT model. Indeed, NRC's current regulations are insufficiently protective, as those regulations allow cancer risks from ionizing radiation far higher than that permitted for any other carcinogen. We should continue to follow the LNT model and to enforce "As Low As Reasonably Achievable" principles. These petitions have now had their public hearing and the NRC should summarily reject them and move on to the many pressing matters of nuclear safety before the agency.

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ATTN: Rulemaking and Adjudications Staff

SUBJECT: Docket ID NRC-2015-0057

This letter transmits the comments of the U.S. Environmental Protection Agency on the petitions for rulemaking filed with the U.S. Nuclear Regulatory Commission concerning Linear No-Threshold Model and Standards for Protection against Radiation (PRM-20-28, PRM-20-29 and PRM-20-30). Thank you for the opportunity to review and comment on these petitions.

Sincerely,

Jonathan D. Edwards
Director
Radiation Protection Division

Enclosure

cc: Josie P. Piccone
Vince H. Holahan

U.S. Environmental Protection Agency's Comments on Linear No-Threshold Model and Standards for Protection against Radiation; Notice of Docketing and Request for Comment ID: NRC-215-0057-0010

The U.S. Environmental Protection Agency strongly disagrees with the petition to the Nuclear Regulatory Commission (NRC) to cease using the linear no-threshold (LNT) model as a basis for regulating exposures to ionizing radiation. The EPA's Carcinogen Assessment Guidelines [1] specify that LNT should be used as a default assumption unless there is compelling evidence that the biological mechanism for carcinogenesis is inconsistent with LNT. More specifically, the Guidelines state: "The linear approach is used when a view of the mode of action indicates a linear response, for example, when a conclusion is made that an agent directly causes alterations in DNA, a kind of interaction that not only theoretically requires one reaction but also is likely to be additive to ongoing, spontaneous gene mutation." Ionizing radiation clearly falls into this category.

Of all the agents demonstrated to be carcinogenic, the evidence for LNT is particularly strong for ionizing radiation. Within limitations imposed by statistical power, the available (and extensive) epidemiological data are broadly consistent with a linear dose-response for radiation cancer risk at moderate and low doses. Biophysical calculations and experiments demonstrate that a single track of ionizing radiation passing through a cell produces complex damage sites in DNA, unique to radiation, the repair of which is error-prone. Thus, no threshold for radiation-induced mutations is expected, and, indeed, none has been observed.

Over the last half century, numerous authoritative national and international bodies have convened committees of experts to examine the issue of LNT as a tool for radiation regulation and risk assessment. These include the U.S. National Academy of Sciences (NAS), the National Council on Radiation Protection and Measurements (NCRP), the International Commission on Radiological Protection (ICRP), and the United Nations Scientific Committee on the Effects of Ionizing Radiation (UNSCEAR). Again and again, these bodies have endorsed LNT as a reasonable approach to regulating exposures to low dose radiation. One exception was a French National Academy Report [2], which found low-dose radiobiological effects in vitro indicative of nonlinearity in the dose response. The most recent NAS report on the subject, BEIR VII [3], reviewed the available data and came to a very different conclusion. The BEIR VII study, which was sponsored by several federal agencies including the EPA and the NRC, determined that "the balance of evidence from epidemiologic, animal and mechanistic studies tend to favor a simple proportionate relationship at low doses between radiation dose and cancer risk." This is the position adopted by the EPA [4] after review by the Agency's Scientific Advisory Board, an independent group of distinguished outside scientists.

Since publication of BEIR VII, additional evidence has accumulated supporting the use of LNT to extrapolate risk estimates from high acute doses to lower doses and dose rates. In this connection, we would note, *inter alia,* results of epidemiological studies on: nuclear workers in the United States, France and the United Kingdom [5]; residents along the Techa River in Russia who were exposed to radionuclides from the Mayak Plutonium Production Plant [6,7]; and children who had received CT scans [8]. These studies have shown increased risks of leukemia and other cancers at doses and dose rates below those which LNT skeptics have maintained are harmless – or even beneficial.

Given the continuing wide consensus on the use of LNT for regulatory purposes as well as the increasing scientific confirmation of the LNT model, it would be unacceptable to the EPA to ignore the recommendations of the NAS and other authoritative sources on this issue. The EPA cannot endorse basing radiation protection on poorly supported and highly speculative proposals for dose thresholds or doubtful notions concerning protective effects from low-level ionizing radiation. Accordingly, we would urge the NRC to deny the petition.

References:

1. EPA. *Guidelines for Carcinogen Risk Assessment.* Risk Assessment Forum, EPA/630/P-03/001F, March, 2005.

2. Tubiana et al., *Dose-Effect Relationships and Estimation of the Carcinogenic Effects of Low Doses of Ionizing Radiation.* Academy of Medicine (Paris) and Academy of Science. Joint Report No. 2, 2005.

3. NAS (National Academy of Sciences). *Health Risks from Exposure to Low Levels of Ionizing Radiation. BEIR VII. Phase 2.* National Academy Press, 2006.

4. EPA. *EPA Radiogenic Cancer Risk Models and Projections for the U.S. Population.* Office of Radiation and Indoor Air, EPA 402-R-11-001, April, 2011.

5. Leuraud et al., Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): and international cohort study, *Lancet Haematol,* published online June 22, 2015 at: http://dx.doi.org/10.1016/S2352-3026(15)00094-0.

6. Krestinina et al., Leukemia incidence among people exposed to chronic radiation from the contaminated Techa River, 1953-2005. *Radiat Environ Biophys,* published online December 12, 2009: DOI 10.1007/s00411-009-0257-5.

7. Davis et al., Solid cancer incidence in the Techa River Incidence Cohort: 1956-2007, *Radiat Res* **184**, 56-65 (2015).

8. Pearce et al., Radiation exposure from CT scans in childhood and subsequent risk of leukemia and brain tumours: a retrospective cohort study, *Lancet,* published online June 7, 2012: DOI:10.1016/S0140-6736(12)60815-0.

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

Issued June 4, 2001

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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The Council wishes to express its appreciation to the Committee members for the time and effort devoted to the preparation of this Report and to the U.S. Nuclear Regulatory Commission for its financial support of this activity.

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.