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MEMORANDUM: Implications of Recent Epidemiologic Studies for the Linear Nonthreshold Model and Radiation Protection

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[13] The National Council on Radiation Protection and Measurements (NCRP) convened Scientific Committee SC 1-25 of experts to review recent epidemiologic studies of low-LET radiation, primarily at low doses or low dose rates, and evaluate whether the new observations provide support for the LNT model as used in radiation protection today. The NCRP Committee members are the authors of this memorandum.

[a] Correspondence: Roy E. Shore, email hrshore@gmail.com. RE Shore and LT Dauer were Chair and Co-chair, respectively, of NCRP Scientific Committee SC 1-25 that produced NCRP Commentary No. 27.

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Highlights

- NCRP Commentary No. 27 focuses on low-dose or low dose-rate radiation exposures to evaluate if recent epidemiologic studies of solid cancer and leukemia risk support the use of the linear nonthreshold (LNT) model for radiation protection purposes.
- The Commentary critically reviews the strengths and weaknesses of the epidemiology, dosimetry and statistics of 29 studies of low-LET radiation with regard to quality and to degree of support for the LNT model.
- While uncertainties remain, NCRP judges that the epidemiologic evidence favors the application of the LNT dose-response model for low-level exposures as a prudent approach to radiation protection.

Abstract

The recently published NCRP Commentary No. 27 evaluated the new information from epidemiologic studies as to their degree of support for applying the linear nonthreshold (LNT) model of carcinogenic effects for radiation protection purposes [1]. The aim was to determine whether recent epidemiologic studies of low-LET radiation, particularly those at low doses and/or low dose rates (LD/LDR), broadly support the LNT model of carcinogenic risk or, on the contrary, demonstrate sufficient evidence that the LNT model is inappropriate for the purposes of radiation protection. An updated review was needed because a considerable number of reports of radiation epidemiologic studies based on new or updated data have been published since other major reviews were conducted by national and international scientific committees. The Commentary provides a critical review of the LD/LDR studies that are most directly applicable to current occupational, environmental and medical radiation exposure circumstances. This Memorandum summarizes several of the more important LD/LDR studies that incorporate radiation dose responses for solid cancer and leukemia that were reviewed in Commentary No. 27. In addition, an overview is provided of radiation studies of breast and thyroid cancers, and cancer after childhood exposures. Non-cancers are briefly touched upon such as ischemic heart disease, cataracts, and heritable genetic effects. To assess the applicability and utility of the LNT model for radiation protection, the Commentary evaluated 29 epidemiologic studies or groups of studies, primarily of total solid cancer, in terms of strengths and weaknesses in their epidemiologic methods, dosimetry approaches, and statistical modeling, and the degree to which they supported a LNT model for continued use in radiation protection. Recommendations for how to make epidemiologic radiation studies more informative are outlined. The NCRP Committee recognizes that the risks from LD/LDR are small and uncertain. The Committee judged that the available epidemiologic data were broadly supportive of the LNT model and that at this time no alternative dose-response relationship appears more pragmatic or prudent for radiation protection purposes.

1. Introduction

The U.S. National Council on Radiation Protection and Measurements (NCRP) convened a scientific committee of experts (SC 1-25) to address the appropriateness of applying the linear nonthreshold (LNT) model to radiation induced cancer for radiation protection purposes, as judged from recent radiation epidemiologic studies of low linear energy transfer (low-LET) radiation exposures. This Memorandum summarizes the key points of the resulting NCRP Commentary No. 27 [1].

The several national and international reviews [2, 3] in the last few decades of the health risks associated with exposure to low levels of ionizing radiation have generally considered that risk estimates based on human epidemiologic data on cancer induction at acute doses of 100 mGy and above are more reliable than estimates based on data <100 mGy, the low-dose region, or at any dose received at a low dose rate [4]. Nevertheless, data derived from studies of low dose or low dose-rate (LD/LDR) exposures provide a direct assessment of possible risks relevant to contemporary radiation exposures. For the purpose of Commentary No. 27, which focused on low-LET radiation, a low absorbed dose is defined as <100 mGy delivered acutely or accumulated over time, and a low absorbed dose rate is defined as <5 mGy h^{-1} for any accumulated dose [4].

The shape of the dose-response relationship and the level of risk from LD/LDR exposures is not well defined for low-LET radiation because of the intrinsic uncertainties in epidemiologic and radiobiologic studies of possible effects. How these uncertainties are handled can influence actions taken regarding radiation protection guidance, medical practice, compensation programs, environmental contamination issues, technological advances, and communication of risk associated with low-level radiation exposure [5]. For over 40 years the LNT dose-response model has been used for practical and prudent guidance on ways to protect workers and the public from the potential harmful effects of low-LET radiation in balance with the beneficial, justified, and optimized uses of radiation. Though no model can be proven to be "correct" given the uncertainties inherent in the epidemiologic LD/LDR data, the primary question is whether the LNT model remains appropriate for radiation protection purposes.

Around a decade ago, both the BEIR VII [3] and UNSCEAR [2] committees reviewed epidemiologic studies of cancer risk from low-LET irradiation, with a large fraction of the studies being based on acute exposures to moderate and high doses. A considerable number of results for updated or new cohorts, many of them with LD/LDR exposures, have been reported since then. The focus of NCRP Commentary No. 27 was on LD/LDR epidemiologic studies, but also included recent studies of Japanese atomic bomb survivors for comparison and as these relate to risks at acute low doses. The aim was to determine whether these epidemiologic studies broadly support the LNT model of carcinogenic risk or, on the contrary, demonstrate sufficient evidence that the LNT model is inferior to some other model for the purposes of radiation protection. The strength of epidemiologic support for the LNT model was evaluated for LD/LDR studies of the incidence of, or mortality from, solid cancer or leukemia. While it was recognized that different types of cancer have different dose-response relationships (and some cancers have not been consistently associated with radiation [2]) and that combining diverse cancers with different etiologies and cell types is not biologically optimal, the limited statistical power of data available for most specific cancer types required a pragmatic approach for radiation protection of using groupings of all solid cancers combined and leukemias (excluding chronic lymphocytic leukemia, "non-CLL leukemia"). Brief consideration was given to LD/LDR studies of thyroid, breast and childhood cancer. Non-cancers also are touched upon briefly: ischemic heart disease, cataracts, and heritable genetic effects.

2. Study Reviews

The studies selected for review focused on LD/LDR studies. The selection was by consensus of the Committee which included experts with a broad purview of the recent radiation epidemiology literature. The selection also was checked against recent comprehensive meta-analyses of such studies [6]. The studies consisted of relatively large cohorts with individual dosimetry and radiation dose-response risk coefficients for total solid cancer, individual cancers or non-CLL leukemia. Earlier reports containing redundant data were eliminated. Analyses of the Japanese Life Span Study of atomic bomb survivors and

LD/LDR studies of exposed groups or tumor sites of special interest (fallout, *in utero* and early childhood exposures; breast cancer, thyroid cancer) also were included. Twenty-nine major studies were critically reviewed.. The critiques included an assessment of the quality of the epidemiology, dosimetry, and statistics of individual studies. The epidemiologic critiques included a characterization of the study design and study population, quality of the data available, data collection methodology and success rates, the degree to which potential confounding variables or biases were assessed, and the quantitative results. The evaluation of the dosimetry of each study included the completeness and precision of the dose information (gamma, neutron and internal exposures) over time for worker studies, the quality of dose reconstruction for applicable studies such as environmental and medical, and the estimation and incorporation of dose uncertainties in determining the shape of the dose-response curve for LD/LDR studies [7]. Statistical evaluations considered whether the analytic methods were appropriate, whether the study considered statistical alternatives to a linear dose-response trend, and whether sensitivity analyses or other clarifying analyses were undertaken. Based on those considerations and on the observed dose-response results, the strength of the study's support for the LNT model as a basis for radiation protection was characterized. Several key studies of radiation and the mortality or incidence of solid cancer and non-CLL leukemia are summarized below.

2.1 Life Span Study

Although the Commentary focused primarily on LD/LDR studies [1], the Life Span Study (LSS) of the Japanese atomic bomb survivors was included as a comparison study. Of note, however, is that about two-thirds (~68,000) of the LSS cohort received estimated colon doses <100 mGy, i.e., low doses. The LSS cohort has provided important data because it is a fairly large cohort (86,661 survivors of all ages) with relatively accurate dosimetry [8], a wide dose range (0 to 4 Gy colon absorbed dose), over 50 years of high-quality follow-up for mortality and cancer incidence, and over 1,000 excess cancer cases estimated to be associated with radiation exposure [9-11]. These features yield good statistical power and narrow confidence intervals (i.e., good precision) of risk estimates for aggregated groupings of all solid cancers

and leukemia. A pure quadratic model for solid cancer provided a significantly poorer fit than a linear dose-response model, although there was evidence of curvilinearity in these data [9, 10].

The most recent solid cancer mortality and incidence data provide some evidence for upward curvature in the dose response consistent with a linear-quadratic model. This implies a shallower, but still positive, dose-response slope at lower doses than at higher ones, although most notably for incidence data [9], this curvilinearity appeared to be confined to males; for females the dose response was essentially linear. The reasons for this sex difference in curvature are yet to be established, though it may partly have to do with divergent profiles of tumor types [9][12]In summary, the study continues to provide support for the use of a LNT model in radiation protection, with consideration that the slope may be lower though still positive at lower doses. However, unlike most other studies reviewed in NCRP Commentary No. 27, the LSS estimates the effects of a single, brief exposure which may not directly apply to protracted or highly-fractionated exposures.

2.2 Worker Studies

Radiation worker studies assess risks in worker groups who largely received low cumulative doses at low dose-rates, and these studies were used to address directly the appropriateness of the LNT model for low dose-rate exposures. Some of the studies have reasonably high statistical power, in part because substantial numbers of workers employed during the 1940s, 1950s and 1960s received cumulative doses over their working lives that were several hundred mGy. However, most studies have low, inadequate statistical power when considered alone because of mostly low cumulative doses, small numbers of workers or short lengths of follow-up. The pooling studies [13] and meta-analyses of studies of cohorts of radiation workers [6] provide increased statistical precision in the estimation of risk. Two of the more informative worker studies are summarized below.

INWORKS Study: The most informative study of pooled cohorts is the International Nuclear Workers Study (INWORKS) that included 308,000 workers from nuclear facilities in the United Kingdom, United States and France [13-18]. INWORKS examined mortality from various causes in relation to cumulative photon doses (mainly gamma radiation) from external sources, and the consortium expended

considerable effort to improve and harmonize the dose estimates [19, 20]. Although they estimated that photon dose uncertainties were small, intrinsic uncertainties remain, especially for workers in the 1940s and 1950s, such as "missed" film badge doses due to recording doses below the limit of detection as zero or recording doses below the limit of detection as the minimally detectable dose, and doses from neutron and internal exposures were not included [19]; these doses could be positively correlated with recorded photon doses leading to an overestimation of the slope of the dose-response. The reported mean cumulative colon dose to exposed workers from photons was 20.9 mGy. Estimated external photon dose to the colon was associated with mortality from all solid cancers combined, with an excess relative risk (ERR) Gy^{-1} of 0.47, 90% confidence interval (CI) of 0.18 to 0.79 [13]. This risk estimate is greater than, but statistically compatible with, the solid cancer mortality ERR Gy^{-1} estimate of 0.35 (95% CI 0.24, 0.47) for the matched (on sex, age at initial exposure and attained age) risk from the LSS (see [6]). For solid cancers there was little evidence of nonlinearity ($p = 0.44$) or of a dose threshold. When the cumulative colon dose was restricted to <100 mGy, a marginally significant dose response was calculated for all cancers excluding leukemia (ERR Gy^{-1} of 0.8, 90% CI 0.01, 1.6) [13]. The recently published site-specific results [18] suggest some caution, however, when interpreting the combined solid cancer analyses because of statistically significant associations between radiation dose and mortality from specific cancers that have not previously been convincingly linked to radiation (testes, rectum, and peritoneum), and a positive association with radiation was reported for cancers that have been linked primarily to asbestos exposure (pleura and mesothelioma) which might occur for work around thermal insulation. These associations suggest there may be confounding in the data. INWORKS investigators also reported an association between the cumulative external photon dose to the red bone marrow (RBM) and mortality from non-CLL leukemia with an ERR Gy^{-1} of 3.0 (90% CI 1.2, 5.2) [14].

Mayak Study: The Russian Mayak cohort of over 25,000 workers is of interest because of the high cumulative external doses received, mainly at low dose rates, by many workers during the early years of operations at this installation (mean cumulative colon dose from external sources of 354 mGy). About 80% of the annual doses for individuals were based on dosimetric measurements, the remainder from dose

reconstructions; extensive work has been ongoing to improve these worker dose estimates [21, 22]. Estimated corrections were made to the early unfiltered film badges for the range of photon energies, angular responses and high-energy beta exposures, and neutron exposures were reconstructed [23]. Nonetheless, uncertainties in external doses remain, particularly for those employed in earlier years of operations, and the substantial doses possible from any intakes of plutonium add a further complication. Investigators reported statistically significant associations between external colon dose and mortality from all solid cancers excluding lung, liver and bone (*i.e.*, these cancers at the major sites of plutonium deposition were excluded) and adjusting for plutonium exposure; the ERR Gy^{-1} was 0.12 (95% CI: 0.03 to 0.21). When the analysis was restricted to workers with little potential for exposure to plutonium, the ERR Gy^{-1} became 0.19 (95% CI 0.02, 0.39) [24]. These risk estimates were less than the solid cancer mortality estimate of ERR Gy^{-1} 0.43 (95% CI 0.30, 0.56) for the matched risk in the LSS [6]. There was no statistical indication of nonlinearity ($p > 0.5$) although the degree of risk below several hundred mGy was uncertain [25]. For incidence of non-CLL leukemia the linear ERR Gy^{-1} estimate was 3.57 (90% CI 1.55, 8.22) for cumulative external radiation dose to the red bone marrow (RBM), adjusted for plutonium exposure [26]. The linear-quadratic model fitted marginally better for non-CLL leukemia than the linear model ($p = 0.11$), and the pure linear and pure quadratic models fitted about equally well. New reports are planned based on extended follow-up and further improvements in the dosimetry, with dose uncertainties taken into account in the risk estimates [21, 22, 27].

Summary of Worker Studies: Other worker studies reviewed included Japanese [28], Canadian [29], U.S. Mound [30] and U.S. Rocketdyne [31] nuclear workers, Russian Chernobyl clean-up workers [32], U.S. radiologic technicians [33], French uranium processing workers [34], Chinese medical x-ray workers [35] and U.S. atomic veterans [36]. Although the accuracy of the risk estimates is limited to various degrees by uncertainties in dosimetric and epidemiologic factors, the strongest nuclear worker studies lend support to the inference that an excess risk of cancer exists following exposure to mainly low doses received at low dose rates. The dose-response data are broadly supportive of an LNT model for radiation protection purposes, perhaps modified by a dose rate effectiveness factor (DREF). (A DREF > 1

means the dose-response slope of the effect for low dose-rate exposures is smaller, by a factor of 1/DREF, than the slope of a study with higher acute doses, typically the LSS.) Further follow-up of these cohorts, along with additional cohorts within the Million Person Study, currently underway in the United States [37, 38], should, in the next few years, appreciably augment the information available on radiation-related cancer risks in groups of workers and consequently reduce the uncertainties in risk estimation after exposures at low dose rates [39, 40].

2.3 Environmental Exposure Studies

The worker studies are complemented by those on environmental exposures, of which several of the more important studies are summarized here.

Techa River Study: Between 1949 and 1956 the Russian Mayak nuclear weapons facility released radioactive waste into the Techa River and exposed approximately 30,000 residents living downstream to doses received at low dose rates from external sources of gamma rays and internally from ^{137}Cs and ^{90}Sr. Considerable efforts have been made to develop individual dose reconstructions for residents (mean dose 35 mGy, range ~0 to 960 mGy) [41].The recent studies of the Techa River Cohort have found associations between radiation dose with incidence [42] or mortality [43] rates for solid cancers. For the 2,300 deaths from solid cancers the linear ERR Gy^{-1} was 0.61 (95% CI 0.04, 1.27) but the shape of the dose-response curve was unclear. For non-CLL leukemia incidence the ERR Gy^{-1} was 2.2 (95% CI 0.8, 5.4) and the linear model provided the best fit [44]. However, uncertainties in the dose reconstruction and cancer ascertainment limit inferences about the shape of the dose-response curves in relation to the LNT model. Further, the tendency for risk to increase with age-at-exposure, and the statistically significant excess of cancers of the uterine cervix, a site not convincingly linked to radiation, and of the esophagus, a site not usually predominant as a radiation effect, add caution to the interpretation of the results [42]. Analyses using improved dosimetry and updated follow-up are underway.

Chernobyl Thyroid Cancer Studies: New studies of cohorts of children in Ukraine and Belarus who had thyroid measurements of ^{131}I activity shortly after the Chernobyl accident and subsequent systematic thyroid screening have added appreciably to our knowledge about thyroid cancer risk after protracted

internal exposure. Both cohorts showed linear dose-response functions with little evidence of nonlinearity [45-47], though with an apparently lower risk per unit dose than seen in studies of children exposed to external radiation at fairly high dose rates [48]. The estimated thyroid doses are reasonably accurate though still uncertain [49], which lends support to a LNT interpretation following childhood exposures.

High Natural Background Radiation Area Studies: Studies of residents in areas of high natural background radiation have been conducted in Kerala, India and Yangjiang, China. The higher quality and larger of the two high natural background radiation studies, the Kerala study of cancer incidence, included 70,000 individuals and over 1,300 cancers from high-background or low-background radiation areas (Nair *et al*., 2009). The dosimetry was based on measurements of ambient levels within and near homes, coupled with estimated age/sex-specific average house-occupancy factors (mean dose 161 mGy, range ~0 to >700 mGy) [50]. The investigators reported an ERR $Gy^{-1}$of –0.13 (95% CI –0.58, 0.46) for all cancer except leukemia [51], and there were too few leukemia cases to be informative. The Yangjiang study reported a positive, but nonsignificant, risk coefficient for mortality from all cancer except leukemia and liver cancer (ERR Gy^{-1} 0.19, 95% CI –1.9, 3.0) [52]; liver cancer mortality was excluded because it appeared to be confounded by geographic variations in diagnosing liver diseases and also the widespread prevalence of hepatitis viral infections. These studies are nominally more supportive of little or no effect after low dose-rate exposures rather than of the LNT model. However, the geographic regions associated with various levels of dose rate may also have variations in lifestyles and other risk factors besides radiation level which could serve to confound the inference regarding radiation effects. Furthermore, the substantial uncertainties in dosimetry, the weaknesses in cancer ascertainment in the regions under study (except perhaps in Kerala which has a cancer registry), and the wide confidence intervals on the risk estimates mean that results need to be interpreted with caution.

2.4 Childhood Irradiation Studies

Diagnostic medical exposures are typically partial body, and study results are subject to significant uncertainties including, but not limited to, poorly documented historical exposure data, limited organ dosimetry for organs other than the target organ, and potential biases because radiologic procedures are

often administered for an existing health condition. Recent epidemiologic studies have involved populations who had received computed tomography (CT) scans during childhood when risk might be greater because individual CT doses were relatively high for diagnostic procedures (though still <100 mGy) and children may be more radiosensitive to cancer induction than adults for some but not all cancer types [53]. The major studies were not limited to childhood exposures but included exposures at ages 0-21 [54] and 0-19 years [55]. A significant deficiency is that information on organ doses from CT examinations in the 1980s and 1990s is sparse and individual doses were not reconstructed in the primary studies [54, 55]. Most importantly, the CT studies suffered from potentially serious biases because the reasons for the examinations were not known, so they could not convincingly address confounding by indication (CT examinations more likely for those who have conditions that confer risk for cancer) and reverse causation (incipient malignancy not detected by the CT examination) [53, 56, 57]. Further studies have now documented the presence of those biases in cohorts receiving CT examinations [58-60], although the impact on results is not yet clear. The CT studies have reported large and essentially linear risk estimates. But, because of the weak dosimetry and potential for bias, the currently available CT epidemiologic study results are inconclusive for evaluating the LNT dose-response model.

The data on postnatal diagnostic x-ray exposures from conventional radiography and childhood leukemia risk are considered inconclusive [61]. Although case-control studies of childhood cancer after diagnostic x-ray exposure *in utero*, involving fetal doses of ~10-50 mGy, are consistent with increased risk for leukemia and other childhood cancers, the interpretation of these studies is not straightforward [61, 62]. Studies of irradiation in childhood or adolescence and subsequent development of breast cancer generally support a linear dose response [53]. A recent pooled analysis of nine studies of external thyroid irradiation in childhood (primarily under age 15 y) and subsequent thyroid cancer showed a strong dose response, even over the range of 0 to 100 mGy, and little evidence of nonlinearity [48]. An analysis of solid cancer incidence among the Japanese atomic bomb survivors exposed before birth or during childhood showed a dose response with marginally significant upward curvature ($p = 0.09$), suggesting that the dose-response slope may be shallower in the low-dose range [63]. In general, the low dose data for children are sparse,

often with limited dosimetry, so uncertainties are substantial. However, the data broadly support the LNT model, especially the data for breast and thyroid cancer.

2.5 Diseases Classified as Tissue Reactions

Most of the available data on noncancer radiation effects, which are generally considered to have dose thresholds rather than being stochastic in nature, have large associated uncertainties and limitations that provide only crude estimates of dose threshold values. Recent epidemiologic evidence, however, suggests the possibility that poorly understood radiobiological mechanisms associated with moderate doses or low dose rates may produce an increased risk of CVD [1, 64]. Studies of nuclear workers and other exposed groups provide an inconsistent picture of CVD risk, and most of them lack information on important potential confounding variables associated with lifestyle and medical risk factors (*e.g.*, diabetes, obesity, smoking). Therefore, the NCRP committee considered the current evidence to be too weak and inconsistent to support a LNT model for CVD for the purposes of radiation protection.

Studies of cataracts in the atomic bomb survivors, Chernobyl clean-up workers and other studies have revealed minor lens opacities at doses lower than previously considered to be cataractogenic, but do not yet support an LNT interpretation or an estimate of a specific dose threshold value for effects from either acute or protracted exposures to the lens of the eye. Ophthalmologically detectable opacities are reported at doses of about 0.5 Gy and above, with large uncertainties below this dose, so the appropriateness of a linear, linear-quadratic or dose-threshold model is unresolved [64-66].

3. Results of Study Evaluations

Support by specific studies for any model required adequacy of the study components, which were classified as epidemiologic methods, dosimetric approaches, and statistical modeling. The NCRP Committee evaluated the epidemiologic, dosimetric and statistical components for 29 principal studies or groups of studies of cancer risk using judgments of “strong”, “moderate”, or “weak” for each component, with intermediate scores (e.g., “weak-to-moderate”) also permitted. To summarize study adequacy, 17

(59%) of the studies had no component on which they were scored as weak or weak-to-moderate, 14 (48%) were scored moderate to strong on all three components of evaluation, and 6 (21%) were scored as strong on all three components [1].

The Committee also rated each of the 29 studies or group of studies, which were mostly based on dose-response analyses, for their strength of support for the LNT model [1] as shown in Table 1. Five studies (17%) provided strong support for the LNT model, four (14%) provided moderate support and nine (31%) provided weak-to-moderate support. A rating of moderate versus strong support for LNT often hinged upon the size of the study or other limitations in methods, dosimetry or statistics, and not on indications of nonlinearity. Five (17%) studies provided no support for a LNT interpretation (i.e., the slope of the dose response was essentially zero or negative). Another four (14%) were considered "inconclusive" because they had excessively unreliable data or no dose-response analysis. It should be noted that all the studies being considered, except for the studies of Japanese atomic bomb survivors and of external thyroid irradiation, had exposures at low dose rates or multiple small exposures. Furthermore, the preponderance of study subjects had cumulative doses under 100 mGy. Thus these recent studies are relevant for contemporary radiation protection concerns.

4. Future Improvements

To support additional radiation epidemiology efforts to address the LNT model as used in radiation protection, the NCRP commentary [1] recommended a number of potentially profitable areas of focus for future research. Selected ones are provided here to stimulate further discussions.

Atomic Bomb Survivors: The low-dose data on solid cancer need to be examined in more detail to determine why the dose-response shapes differ between males (linear-quadratic) and females (linear) [9]. Low-dose risks of cardiovascular diseases and various clinical health endpoints also should be evaluated to the extent possible. An examination is needed of whether the LNT model applies to tumors of various organs or organ systems, insofar as statistical limitations permit, to evaluate the generality of the LNT

model across tumor sites. Updated information on cancer risk among those exposed *in utero* and early childhood would help answer the question of whether risks for those two groups are different as well as provide estimates of risks at older ages for these groups. Innovative ways should be considered to facilitate the biomedical community's access to the large repository of blood, urine and tissue samples from individuals with a range of exposure levels, some who likely developed radiation-related diseases. Such collaborations would facilitate the identification of bioindicators of adverse factors that trigger disease development after irradiation and fill gaps in knowledge of how whole-body exposures to radiation cause human cancer and other diseases using this unique biosample repository.

Worker Studies: Much of the statistical power of these studies derives from those workers who have accumulated moderate doses of several hundred mGy over many years. Continuing follow-up of worker cohorts is a high priority, as much of the cancer incidence and mortality is yet to occur at older ages. Doses in the earliest years of operation tended to be highest but also had the greatest uncertainties because many dose recording technologies and procedures were less advanced than they are today. Therefore, more in-depth analysis of early exposures will be valuable to identify, and if possible remedy, any deficiencies in recorded doses. Issues of neutron exposures, internal exposures and "missed" photon doses need to be addressed further. Valid risk estimates depend upon reliable dose estimates, so this area should be pursued vigorously.

Environmental Radiation Studies: Environmental radiation study investigators should make efforts to reduce uncertainties in the individual reconstructed dose estimates and to account for the uncertainties in risk estimates. The Kerala and Yangjiang studies should increase efforts to improve cancer ascertainment and diagnosis and to closely examine sociodemographic, lifestyle and geographic factors that may affect the adequacy of cancer ascertainment and background risks. Collection and storage of biospecimens from strategically defined subgroups with relatively high estimates of cumulative dose, within environmentally exposed cohorts may be useful for future biodosimetry, molecular epidemiology and bioindicator studies.

Other Future Directions: Better integration of dosimetry and epidemiology in study implementation and analysis is needed. Both shared and unshared uncertainties should be provided with the individual

dose estimates and used to adjust risk coefficients and confidence intervals [67-69]. For circulatory effects, it is important to examine diseases with a shared pathogenesis rather than the broad mixtures of cardiovascular diseases, and to carefully address potential confounding factors in epidemiologic studies. For radiation-induced adverse health outcomes generally, an important need is to identify bioindicators central to causal radiogenic disease pathways that can be used to develop biologically-based dose-response models [70, 71]. Analyzing epidemiologic data in conjunction with relevant radiobiological concepts and data has the potential to provide insights about low-dose risk that augment the knowledge gained from the empirical epidemiologic data [4].

5. Discussion

The principal purpose of NCRP Commentary No. 27 [1] was to assess whether the LNT model is appropriate for the purposes of radiation protection given the new epidemiologic evidence available. Quantitative risk coefficients and dose-response relationships for solid cancers based on estimated individual doses have been reported for well over half a million individuals with low dose-rate exposures and mostly low cumulative doses from studies of radiation workers or of populations living in areas with elevated environmental radiation levels [6].

Strengths of the better LD/LDR studies include relatively good quality dosimetry, long follow-up, high rates of cohort mortality/morbidity ascertainment, large numbers of cancers and person-years at risk, attention to potential confounding variables, and proper analysis. Nevertheless, many individual low-dose studies have intrinsically insufficient statistical power and consequent low precision in risk estimation, in large part because the risk of cancer at very low doses is predicted to be very small and is therefore difficult to statistically distinguish from variations in background risk. Further the effect of slight variation in confounding factors has a much greater influence a low compared with higher doses. Conducting pooled studies [13] and meta-analyses [6, 72, 73] has helped address the statistical power limitations, though more abundant data are needed. Both extended follow-up of the available cohorts and

completion of the Million Person Study in the United States will augment the available information in the future [37, 74].

The NCRP Committee recognized that confounding by non-radiation risk factors for diseases of interest could bias study results and diminish consistency among studies. Many of the studies have attempted to address these issues. The analyses of nearly all studies have considered variations in risk by sex, attained age and often age at exposure. Several studies have directly evaluated or adjusted for the influence of possible confounding by medical radiation exposures [43, 75] or lifestyle factors (*e.g.*, smoking) [9, 25, 28, 42, 51, 76]. Other studies have employed indirect approaches to assess whether there might be biases associated with factors for disease risk [13, 29-31, 52, 77-80], and they have largely not reported evidence of confounding by smoking or other factors, although the influence of such factors at the lowest doses could not be completely discounted. A consideration related to this is that lifestyle or other disease risk factors will cause confounding only if their frequency (or intensity) varies consistently by dose.

Although several studies showed null/negative dose-response relations for solid cancer (Table 1) or provided only limited evidence of a positive association at doses under about 100 mGy [32, 43], a variety of studies has shown elevated solid cancer occurrence in the low-dose range [6, 10, 13, 25, 48]. Eleven (38%) studies provided moderate or strong support for the LNT model for radiation protection (Table 1), and other LD/LDR reports indicate dose-related elevations in leukemia risk [14, 26, 44, 81-83]. Thus, the weight of evidence continues to support the use of the LNT model for low doses and dose rates exposures.

NCRP Commentary No. 27 [1] evaluated recent epidemiologic studies as to whether they provided support for the continued use of the LNT model in radiation protection. The purview did not include, however, an evaluation of recent experimental radiation studies on mutations, cytogenetics, cells, and animals or mechanistic understanding which would complete the assessment [4, 84, 85].

6. Conclusions

While the LNT model cannot be scientifically proven by epidemiologic evidence at very low doses or low dose rates, the preponderance of high-quality epidemiologic data is reasonably consistent with the LNT assumption. The current data are not precise enough to exclude models that differ from the LNT model, and there is evidence from some datasets that the slope of the dose response at low levels of exposure may be less than that at higher levels. The NCRP Commentary recognizes that the risks from a few tens of mGy are uncertain and are predicted to be very small. The NCRP judges, in accordance with other national and international scientific committees [2, 3, 86], that the available epidemiologic evidence does not point to any alternate dose-response relationship that would be more pragmatic or prudent for radiation protection purposes than the LNT model. Therefore, NCRP concludes that, based on current epidemiologic data, the LNT model (perhaps with excess risk estimates reduced by a DREF) should continue to be used for radiation protection purposes [1].

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Table 1—Rated strength of support for the LNT model for use in radiation protection by studies of radiation exposure and cancer

Studies (or groups of studies) and representative publications [a,b,c]	Support for LNT Model
Life Span Study (LSS), Japan atomic bombs [9]	Strong
INWORKS (U.K., U.S., French combined cohorts) [13]	Strong
Tuberculosis fluoroscopic examinations and breast cancer [87]	Strong
Childhood Japan atomic bomb exposure [63]	Strong
Childhood thyroid cancer studies [48]	Strong
Mayak nuclear workers [25]	Moderate
Chernobyl fallout, Ukraine and Belarus thyroid cancer [46]	Moderate
Breast cancer studies, after childhood exposure [88]	Moderate
In utero exposure, Japan atomic bombs [63]	Moderate
Techa River, nearby residents [43]	Moderate [d]
In utero exposure, medical [61]	Moderate [d]
Japan nuclear workers [28]	Weak-to-moderate
Chernobyl cleanup workers, Russia [32]	Weak-to-moderate
U.S. radiologic technologists [33, 89]	Weak-to-moderate
Mound nuclear workers [30]	Weak-to-moderate
Rocketdyne nuclear workers [31]	Weak-to-moderate
French uranium processing workers [34]	Weak-to-moderate
Medical x-ray workers, China [35]	Weak-to-moderate [e]
Taiwan radiocontaminated buildings, residents [90]	Weak-to-moderate [e]
Background radiation levels and childhood leukemia [81]	Weak-to-moderate

In utero exposures, Mayak and Techa [91]	No support
Hanford ^{131}I fallout study [92]	No support
Kerala, India, high natural background radiation area [51]	No support
Canadian worker study [29]	No support
U.S. atomic veterans [36]	No support
Yangjiang, China, high natural background radiation area [52]	Inconclusive [e]
CT examinations of young persons [54]	Inconclusive [e]
Childhood medical x rays and leukemia (aggregate of >10 studies) [61, 93]	Inconclusive [e]
Nuclear weapons test fallout studies (aggregate of eight studies) [94]	Inconclusive [e]

[a] Study ratings were based on reported solid cancer (or close surrogates) risk unless noted otherwise.

[b] A representative recent publication is listed for each study or study group. Others are found in the text.

[c] A number of studies were excluded for various reasons, including but are not limited to: ecological studies of residents around nuclear power plant facilities, studies of hereditary effects, studies of tissue reaction (or "deterministic") effects, and the 15-Country study and other studies that overlap with the more recent INWORKS study.

[d] Considered borderline between "Moderate" and "Weak-to-Moderate" support for the LNT model.

[e] Considered "weak" support or "inconclusive" primarily because of weaknesses in epidemiology, dosimetry or statistical risk modeling. The studies listed as "No support" had reasonable methodologies but provided little or no support for the LNT model because their risk coefficients were essentially zero or negative.