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

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Preface

The National Council on Radiation Protection and Measurements (NCRP) has a long history of issuing guidance on operational radiation safety including radiation exposure limits for radiation workers and the public. Effective dose limits are based on the linear nonthreshold (LNT) dose effects model, which is based almost entirely on the human epidemiology data. This Commentary provides a review of recent epidemiologic studies and an evaluation of whether the new observations are strong enough to support or modify the LNT model as used in radiation protection today. This Report represents an update of the guidance provided in NCRP Report No.136, *Evaluation of the Linear-Nonthreshold Dose-Response Model for Ionizing Radiation* (NCRP, 2001).

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President

Contents

Preface 2

1. **Executive Summary** 10
   - 1.1 Introduction 10
   - 1.2 Study Reviews 11
     - 1.2.1 Life Span Study 11
     - 1.2.2 Worker Studies 12
     - 1.2.3 Environmental Exposure Studies 13
     - 1.2.4 High Background Radiation Areas 13
     - 1.2.5 Childhood Radiation Studies 14
     - 1.2.6 Diseases Classified as Tissue Reactions 14
   - 1.3 Results of Study Evaluations 15
   - 1.4 Future Improvements 17
   - 1.5 Summary 18
   - 1.6 Overall Conclusions on the Use of the LNT Model 19

2. **Introduction** 20
   - 2.1 Background 20
   - 2.2 LNT and the Estimation of Cancer Risk 22
   - 2.3 Objective and Scope 23

3. **Important Considerations** 24
   - 3.1 Epidemiologic Considerations 24
   - 3.2 Dosimetry Considerations 27
   - 3.3 Statistical Considerations 29
   - 3.4 Dose-Response Considerations 31
     - 3.4.1 Dose Response and Solid Cancers: Cancer Type and Sensitivity 31
     - 3.4.2 Dose Response and Leukemia 34
     - 3.4.3 DDREF Considerations 34

4. **Review of Epidemiologic Studies of Cancer and Genetic Effects from Low-Dose or Low Dose-Rate Irradiation** 35
   - 4.1 Japanese Atomic-Bomb Survivors 61

109 4.2.6.1 Dosimetry 97

4.2.6.2 Epidemiologic Methods, Findings and Issues 98
4.2.6.3 Study Strengths and Weaknesses 98
4.2.6.4 Implications for the LNT Model and Radiation Protection 99
4.2.7 Million Worker Study 99
4.2.7.1 Introduction 99
4.2.7.2 Dosimetry 100
4.2.7.3 Epidemiologic Methods, Findings and Issues 100
4.2.7.4 Study Strengths and Weaknesses 106
4.2.7.5 Implications for the LNT Model and Radiation Protection 106
4.2.8 Chinese Medical X-Ray Worker Study 106
4.2.8.1 Dosimetry 106
4.2.8.2 Epidemiologic Methods, Findings and Issues 107
4.2.8.3 Study Strengths and Weaknesses 107
4.2.8.4 Implications for the LNT Model and Radiation Protection 107
4.3 Environmental Exposure Studies 108
4.3.1 Techa River Resident Cohort 109
4.3.1.1 Dosimetry 109
4.3.1.2 Epidemiologic Methods, Findings and Issues 110
4.3.1.3 Study Strengths and Weaknesses 113
4.3.1.4 Implications for the LNT Model and Radiation Protection 113
4.3.2 Chernobyl Resident Cohorts 114
4.3.2.1 Dosimetry 114
4.3.2.2 Epidemiologic Methods, Findings and Issues 115
4.3.2.3 Study Strengths and Weaknesses 117
4.3.2.4 Implications for the LNT Model and Radiation Protection 117
4.3.3 High Natural Background Radiation Area (HBRA) Studies: Kerala Study 117
4.3.3.1 Dosimetry 118
4.3.3.2 Epidemiologic Methods, Findings and Issues 118
4.3.3.3 Study Strengths and Weaknesses 120
4.3.3.4 Implications for the LNT Model and Radiation Protection 120
4.3.4 Yangjiang China HBRA Study 121
4.3.4.1 Dosimetry 121
4.3.4.2 Epidemiologic Methods, Findings and Issue 121
4.2.4.3 Limitations of the Kerala and Yangjiang HBRA Studies 122

4.2.4.4 Implications of the HBRA Studies for the LNT Model and Radiation Protection 122
4.3.5 Taiwan Residents of Radiation-Contaminated Buildings 122
4.3.5.1 Dosimetry 122
4.3.5.2 Epidemiologic Methods, Findings and Issues 123
4.3.5.3 Study Strengths and Weaknesses 124
4.3.5.4 Implications for the LNT Model and Radiation Protection 124
4.3.6 Radiation Fallout Studies 124
4.3.6.1 Japanese Atomic-Bomb Fallout 125
4.3.6.2 Marshall Islands Atomic Testing Fallout 125
4.3.6.3 Nevada Test Site (NTS) Atomic Fallout in Utah 126
4.3.6.4 Atomic Testing Fallout Across the United States 127
4.3.6.5 Semipalatinsk Fallout 127
4.3.6.6 Hanford ^{131}I Fallout 128
4.3.6.7 Mayak Fallout 129
4.3.6.8 Three Mile Island (TMI) Fallout 129
4.3.6.9 Fukushima Dai-ichi Fallout 129
4.4 Medical Exposure Studies 130
4.4.1 TB Fluoroscopy Studies 131
4.4.1.1 Dosimetry 131
4.4.1.2 Epidemiologic Methods, Findings and Issues 132
4.4.1.3 Summary Studies of TB Patients Receiving Repeated Chest Fluoroscopies for Lung Collapse 132
4.4.1.4 Implications for the LNT Model and Radiation Protection 132
4.4.2 Computed Tomography Scanning Studies 132
4.4.2.1 Dosimetry 133
4.4.2.2 Epidemiologic Methods, Findings and Issues 133
4.4.2.3 Strengths and Limitations 134
4.4.2.4 Analyses to Evaluate Biases in CT Studies 135
4.4.2.5 Implications for the LNT Model and Radiation Protection 135
4.5 Childhood Exposure Studies 136
4.5.1 Childhood Atomic-Bomb Survivors 137
4.5.2 Childhood Leukemia Studies 137
4.5.3 Thyroid Cancer Studies 138

4.5.3.1 Pooled Studies of Thyroid Cancer after X- or Gamma Irradiation 138
4.5.3.2 Other Studies of Thyroid Cancer after Childhood Exposure 142
4.5.4 Breast Cancer Studies 142
4.6 *In Utero* Exposure Studies 143
4.6.1 Pregnancy Risks from Ionizing Radiation 144
4.6.2 *In Utero* Exposures to Occupational or Environmental Sources 144
4.6.3 *In Utero* Diagnostic Radiology 146
4.7 Genetic Studies (Heritable Effects in Human Populations) 147
4.7.1 Studies of Atomic-Bomb Survivor Offspring 147
4.7.2 Studies of Offspring after Parental Preconception Radiotherapy 148
4.7.3 Cancer in Offspring after Environmental Preconception Radiation Exposure 149
4.7.4 Implications for Radiation Protection 149

5. Review of Epidemiologic Studies for Tissue Reactions 150
5.1 Cardiovascular Effects Studies 151
5.1.1 Higher Doses and Cardiovascular Disease 152
5.1.2 TB Fluoroscopy Studies 153
5.1.2.1 Dosimetry 153
5.1.2.2 Study Strengths and Weaknesses 153
5.1.2.3 Implications for the LNT Model and Radiation Protection 154
5.1.3 Nuclear Worker Radiation Exposure and Cardiovascular Diseases 154
5.1.4 Environmental Radiation Exposure 160
5.1.5 Implications of Cardiovascular Disease for the LNT Model and Radiation Protection 160
5.2 Cataract Studies 162
5.3 Thyroid Noncancer Effects Studies 162
5.3.1 Atomic-Bomb Studies 163
5.3.2 Chernobyl ^{131}I Fallout and Noncancer Thyroid Effects 163
5.3.3 Other Studies of Radioactive Iodine Fallout and Thyroid Effects 163
5.3.4 Implications of Noncancer Thyroid Effects for Radiation Protection 164

6. Study Quality 165
6.1 Strengths 165

6.2 Opportunities for Improvement 166

7. Strength of Support for LNT in Recent Epidemiologic Studies 167

8. Future Directions 171

8.1 Epidemiology 171

8.1.1 Atomic-Bomb Studies 171

8.1.2 Radiation Worker Studies 173

8.1.3 Environmental Radiation Studies 173

8.1.4 Computed Tomography Studies 174

8.1.5 Childhood and *In Utero* Exposures 174

8.1.6 Studies of Tissue Reactions 175

8.2 Dosimetry: Future Directions 175

8.3 DDREF: Future Directions 176

8.4 Key Events, Bioindicators and Risk Assessment: Future Directions 177

8.5 Other Future Directions/Recommendations 178

9. Conclusions 180

9.1 Overall Conclusion on Use of the LNT Model 180

9.2 Supporting Conclusions 180

9.3 Radiation Protection Implications 181

Glossary 182

Abbreviations, Acronyms and Symbols 187

References 189

1. Executive Summary

1.1 Introduction

Historically, epidemiologic studies have assessed the health effects of ionizing radiation exposure from multiple sources: occupational, accidental, environmental, military and medical. The several national and international reviews of the status of health risks associated with exposure to low levels of ionizing radiation that have been completed in the last few decades generally agreed that the expectations for health effects in humans, such as cancer induction or cardiac damage, observed at acute doses of 100 mGy and above are more reliable than those observed at <100 mGy, the low-dose region (NCRP, 2015). For the purpose of this Commentary, for low linear-energy transfer (LET) radiation, a low absorbed dose is <100 mGy delivered acutely, and a low absorbed-dose rate is <5 mGy h^{-1} for any accumulated dose. See NCRP Commentary No. 24 (NCRP, 2015) Section 1.1 for additional discussion of low doses and low dose rates.

Our understanding of the shape of the dose-response relationship and the level of risk from low-LET types of radiation at low doses and low dose rates remains uncertain because of the intrinsic uncertainties in results from the epidemiologic and radiobiological studies of low doses of radiation. This uncertainty can impact actions taken regarding radiation protection guidance, medical practice, compensation programs, environmental contamination issues, technological advances, and communication with members of the public (NCRP, 2015). For over 40 y the linear nonthreshold (LNT) dose-response model has been commonly utilized for low-LET radiation when developing practical and prudent guidance on ways to protect workers and the public from the potential for harmful effects from radiation while balancing the beneficial, justified, and optimized uses of radiation in our society. Indeed, in developing its basic recommendations, as currently given in NCRP Report No. 116 (NCRP, 1993a), the Council reiterated its acceptance of the LNT model for the purposes of radiation protection.

The purpose of this Commentary is to provide a review of recent data from studies with low dose rates and from the Life Span Study of atomic-bomb survivors to determine whether these epidemiologic studies broadly support the LNT model of carcinogenic risk or, on the contrary, whether there is sufficient evidence that the LNT model is inappropriate for the purposes of radiation protection. The strength of epidemiologic support for the LNT model is evaluated for solid cancer incidence or mortality and secondarily for low dose-rate studies of leukemia. Briefer consideration is also given to low dose studies of thyroid cancer and breast cancer. The focus of this commentary is on low doses and low dose rates.

1.2 Study Reviews

The primary approach was a critical review of each major study. The critique included an assessment of the quality of the epidemiology, dosimetry, and statistics of each study. The epidemiologic evaluation included a characterization of the study design and study population, quality of the data available, data collection methodology, the degree to which potential confounding variables or biases were assessed, and the quantitative results. Analysis of the dosimetry helped evaluate the robustness of the study in supporting the shape of the dose response curve at low doses and low dose rates. A statistical evaluation 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, the contribution the study makes to the LNT model and to radiation protection is characterized. Several key studies about solid cancer mortality or incidence are briefly summarized below.

1.2.1 *Life Span Study*

Although this report focuses on studies with low doses and low dose rates, the Life Span Study (LSS) was included as a benchmark comparison study. The LSS cohort of atomic-bomb survivors (Section 4.1) has provided important data because it is a large cohort (~86,000 survivors of all ages) with relatively accurate dosimetry, a wide dose range (0 to 4 Gy colon dose, including ~68,000 with doses <100 mGy), over 50 y of high-quality follow-up for mortality and cancer incidence, and over 1,000 excess cancer cases associated with radiation exposure. These features provide relatively high statistical power and precision of risk estimates, resulting in a statistically significant dose response for all incident solid cancer over the dose range 0 to 100 mGy (Grant *et al*., 2017). Formal dose-threshold analyses for both solid cancer incidence and mortality are compatible with no dose threshold, and a pure quadratic model provided a significantly poorer fit than a linear dose-response model (Grant *et al*., 2017; Ozasa *et al*., 2012).

A nonparametric analysis of the most recent mortality data indicated excess risk over the range of 0 to 200 mGy that was congruent with the LNT dose response model. Nevertheless, 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 low doses than at higher ones, though this curvilinearity appeared to be confined primarily to males. In summary, the study provides strong support for the use of a LNT model, with consideration of a low-dose effectiveness factor (LDEF), for use in radiation protection. However, unlike most other studies reviewed in this report, the LSS assesses the effects of a single, brief exposure and the associated LDEF, but it does not assess protracted or highly-fractionated doses.

1.2.2 *Worker Studies*

Radiation worker studies assess risks in worker groups exposed largely to low doses received at low dose-rates, addressing directly the validity of the LNT model for low dose-rate exposures. Further, cumulative doses can be several hundred mGy, especially for workers in early periods, so that some studies can offer reasonable statistical power.

INWORKS Study: Large studies that combine data from workers from numerous nuclear installations in a number of countries have now been conducted (Cardis *et al*., 1995; 2007). An important study is the International Nuclear Workers Study (INWORKS), which included workers from nuclear facilities in the United States, United Kingdom, and France (Leuraud *et al*., 2015; Hamra *et al*., 2016; Richardson *et al*., 2015) (reviewed in Section 4.2.2). INWORKS found an association between the cumulative external photon dose to the red bone marrow (RBM) and mortality from leukemia [excluding chronic lymphocytic leukemia (CLL) excess relative risk (ERR) Gy^{-1} of 3.0, 90 % confidence interval (CI) of 1.2 to 5.2]. External dose to the colon (used as the prototypic organ) was associated with mortality from all solid cancers combined (ERR Gy^{-1} of 0.47, 90 % CI of 0.18 to 0.78). For solid cancer there was no evidence of nonlinearity ($p = 0.44$). These risk estimates were similar to those in the LSS data. Even when the cumulative colon dose was restricted to 0 to 100 mGy, a statistically significant dose response was seen for all cancers excluding leukemia.

Mayak Study: The Russian Mayak workforce is of particular interest because of the high cumulative doses received (mainly at a low dose rate) by many workers during the early years of operations at this installation (Section 4.2.3). The investigators reported statistically significant associations between external dose and mortality from leukemia (excluding CLL) and from all solid cancers excluding lung, liver and bone (*i.e*., excluding cancers at the major sites of plutonium deposition); and adjusting for plutonium exposure; ERR Gy^{-1} of 0.12, 95 % CI: 0.03 to 0.21 (Sokolnikov *et al*., 2015). For solid cancer there was no indication of nonlinearity ($p > 0.5$) based on external dose to the colon. For leukemia, excluding the chronic lymphocytic type, 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, adjusted for plutonium exposure. The linear-quadratic model fit marginally better than the linear model ($p = 0.11$), and the pure linear and pure quadratic models fit about equally well.

Summary of Worker Studies: Overall the nuclear worker studies lend considerable support to the inference that an excess risk of cancer exists following protracted exposure to low doses received at a low dose rate, and the excess risk is compatible with a LNT model, perhaps modified by a DDREF. Although the accuracy of the risk estimates is

limited to some degree by uncertainties in dosimetry and epidemiology, the studies provide substantial support for the LNT model. The Million Worker Study is underway in the United States; when it is completed it is expected to augment appreciably the information available on worker radiation-related cancer risks and reduce the uncertainties in risk estimation after exposures at low dose rates (Boice, 2015a; 2017c; Boice *et al*., 2014; Bouville et al., 2015; Till *et al*., 2014).

1.2.3 *Environmental Exposure Studies*

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 to relatively low doses at low dose rates from gamma rays (external) and ^{137}Cs and ^{90}Sr (internal). The recent studies of the Techa River Cohort have found associations between radiation dose and incidence and mortality rates for solid cancers and leukemia (other than CLL) that they report are linear in dose response (Davis *et al*., 2015; Krestinina *et al*., 2013a; Schonfeld *et al*., 2013) (Section 4.3.1). However, inherent uncertainties in the dose reconstruction along with some limitation in the cancer ascertainment weaken inferences about the shape of the dose-response curves and the LNT model.

Chernobyl Thyroid Cancer Studies: New studies of cohorts of children in Ukraine and Belarus who had thyroid measurements of ^{131}I shortly after the Chernobyl accident and systematic thyroid screening have added appreciably to our knowledge about thyroid cancer risk after protracted internal exposure (Brenner *et al*., 2011; Zablotska *et al*., 2011) (Section 4.3.2). Both cohorts showed strong linear dose-response functions with no evidence of nonlinearity, though perhaps with a somewhat lower risk per unit dose than seen in studies of children exposed to external gamma radiation. The thyroid doses are believed to be sufficiently accurate to support a LNT interpretation.

1.2.4 *High Background Radiation Areas*

Studies of residents in areas of high natural background radiation have been conducted in Kerala, India and Yangjiang, China. However, it is exceedingly difficult to conduct a geographic study of background radiation, *e.g*., it is difficult to find a suitable low exposure control group with highly similar lifestyles and natural disease rates to whom the highly exposed group may be compared. The better and larger of the two studies, the Kerala study of cancer incidence, included 70,000 individuals and over 1,300 cancers from high-background or low-background areas (Nair *et al*., 2009) (Section 4.3.3). The dosimetry was based on measurements of ambient levels within and near homes, coupled with average house-occupancy factors by age and sex. They reported an ERR Gy^{-1}of –0.13 (95 % CI –0.58, 0.46) for all cancer except leukemia, and there were too few leukemia cases to be informative. The Yangjiang study reported a positive, but nonsignificant, risk coefficient for all cancer except leukemia and liver

cancer [ERR Gy^{-1} 0.19 (95 % CI –1.9, 3.0); Tao *et al*., 2012]. These studies are nominally more supportive of little or no effect after low dose-rate exposures rather than the LNT model. However, the fact that much of the dose variation is attributable to geographic locations, which may be associated with risk factors other than radiation level, introduces ambiguity into the inference regarding radiation effects. Furthermore, the substantial uncertainties in dosimetry, the weaknesses in cancer ascertainment, and the wide confidence intervals on the risk estimates mean they need to be interpreted with caution.

1.2.5 *Childhood Radiation Studies*

Medical exposures are typically partial body and study results are subject to significant uncertainties including, but not limited to, 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 CT doses were relatively high and children may be more radiosensitive to cancer induction than adults (Section 4.4.2). However, information on organ doses from CT examinations in the 1980s and 1990s is sparse and individual doses have not been reconstructed. CT studies suffer from potential biases: confounding by indication (CT examinations more likely for those who have conditions that confer risk for cancer) and reverse causation (pre-existing but undetected malignancy). Because of the weak dosimetry and potential for bias, the results are considered unreliable for evaluating the LNT dose response model.

The data on postnatal diagnostic medical exposures and childhood leukemia risk are inconclusive (Wakeford, 2008). Studies of juvenile irradiation and breast cancer generally support a linear dose response. A recent pooled analysis of external thyroid irradiation in childhood and subsequent thyroid cancer in nine studies showed a significant dose response from 0 to 100 mGy and no evidence of nonlinearity (Lubin *et al*., 2017). An analysis of solid cancer incidence among the Japanese atomic-bomb survivors exposed prenatally or during childhood showed a clear dose response, but marginal upward curvature ($p = 0.09$) suggested that the dose-response slope may be shallower in the low-dose range. In general, the low dose data on children are sparse, the number of specific types of cancer is small and uncertainties are large enough that such studies do not yield definitive information on the LNT model. In the case of thyroid cancer and breast cancer, the data broadly support the LNT model.

1.2.6 *Diseases Classified as Tissue Reactions*

Most of the available data on noncancer effects have large associated uncertainties and limitations that do not yet support a quantitative estimate of a specific threshold value for effects from either acute or protracted lens

exposures. However, the preponderance of evidence suggests the possibility that effects (such as lens opacities or cardiovascular disease) could occur at lower doses than previously thought.

There is growing epidemiologic evidence to suggest a raised risk of cardiovascular disease (CVD) at lower levels of exposure to radiation than previously thought, implying that poorly understood radiobiological mechanisms associated with low-to-moderate doses and/or low dose rates may produce an increased risk of CVD (Section 5.1). Studies of nuclear workers and other exposed groups provide a mixed picture as to CVD risk, and most of them lack information on important confounding factors associated with lifestyle and concurrent conditions (*e.g.*, diabetes, obesity). Therefore, the evidence is too weak and inconsistent to support a LNT model for CVD at this time.

Studies of cataracts in the atomic-bomb survivors and following Chernobyl exposures have revealed the development of minor lenticular opacities at doses lower than previously considered to be cataractogenic. Ophthalmologically detectable opacities are reported at doses of 0.5 to 2 Gy with large uncertainties below about 0.5 Gy. So, at this time, the NCRP recommends use of a threshold model for cataracts (NCRP, 2016).

1.3 Results of Study Evaluations

Support by studies for any model requires adequacy of the study components, which for epidemiologic studies can be classified broadly as adequacy of epidemiologic methods, dosimetry, and statistics. For each component of the major studies, this commentary has critiqued both the methods used and the adequacy of the results of those methods (Section 7). The Committee evaluated these components for 26 principal studies or groups of studies of cancer risk. As a minimal criterion of study adequacy, 18 of the studies had no component on which they were scored as weak. Thirteen of the studies were scored moderate to strong on all three components of evaluation.

The Committee also rated each study or group of studies on their strength of support for the LNT model, as shown in Table 1.1. Twenty-one studies (80 %) provided some support for the LNT model, including five studies (19 %) providing strong support and seven providing moderate support.. Five of the studies (19 %) provided essentially no or inconclusive support for the LNT model. A rating of moderate versus strong support for LNT sometimes hinged upon the size of the study or other limitation and not on indications of nonlinearity. most of the larger,

Table 1.1—*Ratings of the degree of support for the LNT model by the cancer studies reviewed.*

Study (or groups of studies) a	Support for LNT Model
Life Span Study (LSS), Japan atomic bomb (Grant *et al*., 2017)[b]	Strong
INWORKS (U.K., U.S., French combined cohorts) (Richardson *et al*., 2015)	Strong
Tuberculosis fluoroscopic examinations and breast cancer (Little and Boice, 2003)	Strong
Childhood atomic-bomb exposure (Preston *et al*., 2008)	Strong
Childhood thyroid cancer studies (Lubin *et al*., 2017)	Strong
Mayak nuclear facility (Sokolnikov *et al*., 2015)	Moderate
Techa River, nearby residents Davis *et al*., 2015)	Moderate
Chernobyl fallout, Ukraine and Belarus thyroid cancer (Brenner *et al*., 2011)	Moderate
Breast cancer studies, after childhood exposure (Eidemüller *et al*., 2015)	Moderate
In utero atomic-bomb exposure (Preston *et al*., 2008)	Moderate
In utero exposures, medical (Wakeford, 2008)	Moderate
Canadian worker study (Zablotska *et al*., 2013b)	Moderate
Japanese worker study (Akiba and Mizuno, 2012)	Weak to moderate
Chernobyl cleanup workers, Russia (Kashcheev *et al*., 2015)	Weak to moderate
U.S. radiologic technologists (Liu *et al*., 2014; Preston *et al*., 2016)	Weak-to-moderate
Mound facility (Boice *et al*., 2014)	Weak-to-moderate
Rocketdyne facility (Boice *et al*., 2011)	Weak-to-moderate
Medical x-ray workers, China (Sun *et al*., 2016)	Weak-to-moderate
Background radiation levels and childhood leukemia (Kendall *et al*., 2013)	Weak-to-moderate
Taiwan radiocontaminated buildings, residents (Hwang *et al*., 2008)	Weak-to-moderate[c]
Pediatric CT examinations (Pearce *et al*., 2012)	Weak-to-moderate[c]
Childhood leukemia studies (Wakeford and Little, 2003)	Weak-to-moderate
In utero exposures, Mayak and Techa (Akleyev *et al*., 2016)	Weak-to-moderate
Hanford ^{131}I fallout study (Davis *et al*., 2004)	None
Kerala, India, high natural background radiation area (Nair *et al*., 2009)	None
Yangjiang, China, high natural background radiation area (Tao *et al*., 2012)	Inconclusive[c]
U.S. atomic veterans (Beck *et al*., 2017)	Inconclusive
Fallout studies (aggregate of eight studies) (Lyon *et al*., 2006)	Inconclusive[c]

[a]A number of studies were excluded for various reasons described in the text, these include 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

[b]A representative recent publication is listed for each study or study group.

[c]Considered "weak" support or "inconclusive" primarily because of epidemiologic method or dosimetric weaknesses. The other studies in these categories were reasonable methodologically but provided little or no support for the LNT model because their risk coefficients were essentially zero or negative.

stronger studies broadly supported a LNT model. The studies that provided no support for the LNT model either had a totally null dose response or had excessively unreliable data. It should be noted that all the studies being considered, except for the Life Span Study of atomic-bomb survivors, had exposures at low dose rates or multiple small exposures. Furthermore, the preponderance of study subjects had cumulative doses under 100 mGy. Thus these studies are very relevant for contemporary radiation protection concerns.

1.4 Future Improvements

To stimulate radiation epidemiology efforts to address the LNT model and low- dose risks, the Committee suggested a number of profitable areas of focus for future research (report Section 8), and a few are mentioned here.

Atomic-Bomb Survivors: The low-dose data need to be examined in more detail, using additional covariables, statistical methods and analytic strategies, not only for solid cancer and leukemia, but also to evaluate specific cancers or cancer groups, cardiovascular diseases, and various clinical health endpoints. An examination is needed of whether the dose-response LNT model applies to tumors of various organs or organ systems, insofar as statistical limitations permit, which will provide evidence regarding the generality of the LNT model across tumor sites. The large bank of blood and tissue samples should be studied more robustly by the biomedical community to identify bioindicators of drivers of adverse outcome pathways that mediate between radiation and disease development.

Worker Studies: Much of the statistical power of these studies derives from those workers who have accumulated moderate doses of several hundred milligray over many years, most of whom started work in earlier years. Continuing follow-up of worker cohorts is desirable, as much of the cancer incidence and mortality is yet to occur. Doses in the early years tended to be highest but also had the greatest uncertainties because most dose recording technologies and dose record keeping practices were less advanced. Therefore, scrutiny of dose records is necessary to identify any deficiencies in recorded doses. Issues of neutron exposures, internal exposures and missing doses need to be addressed further. Valid risk estimates depend, inter alia, upon reliable dose estimates, so this area should be pursued vigorously.

Environmental Radiation Studies: All the environmental study groups should consider measures to reduce individual dose uncertainties. The Kerala and Yangjiang studies should increase efforts to improve cancer ascertainment and diagnosis, and to closely examine sociodemographic and geographic factors that may affect the

adequacy of cancer ascertainment. Further validation of reconstructed doses by personal dosimetry measurements would also be valuable. The Techa River studies should continue to improve dosimetry, enhance their follow-up and outcome ascertainment and further address the medical exposures received.

Other Future Directions: Uncertainties should be provided with the dose estimates and used to adjust risk coefficients and confidence intervals (Stram *et al*., 2015; UNSCEAR, 2015). For radiation-induced adverse health outcomes, a clear need is to identify bioindicators that define the pathway from normal to malignant cells that can be used for developing biologically based dose-response models. Analyzing epidemiologic data in conjunction with relevant radiobiological concepts and data has the potential to provide insights about low-dose risk that augment knowledge gained from the empirical epidemiologic data in isolation (NCRP, 2015).

1.5 Summary

Quantitative solid cancer risk estimates, based on estimated individual doses, of cancer mortality or incidence have been reported for nearly one million individuals with low dose rates and mostly low doses from studies of radiation workers or those exposed to elevated environmental radiation levels (Shore *et al*., 2017). The completion of the million person study will considerably augment the available information (Boice, 2012a). The more robust studies have many strengths, with relatively good quality dosimetry, high rates of cohort mortality/morbidity ascertainment, attention to potential confounding variables, and proper analysis. Nevertheless, it is recognized that all studies have limitations, ranging from minor to serious, in their contribution to the quantitative evaluation of the LNT model. The individual low- dose studies intrinsically have limited statistical power and precision in risk estimation. These studies complement the LSS study of atomic-bomb survivors with its high dose rate and high dose range.

Strengths of some of the large epidemiologic studies such as INWORKS and the LSS lie in the long follow-up and large numbers of cancers and person-years at risk. The length of follow-up of epidemiologic studies is particularly relevant since a large fraction of both spontaneous and radiation-related cancers occur at 60 y of age and beyond. Although an historic weakness of many worker and environmental radiation studies was inadequate dosimetry, in recent years investigators have been focusing more on improving the quality and accuracy of the dosimetry. However, most studies considered in this report did not consider the effects of shared vs unshared uncertainty and classical as opposed to Berkson error (UNSCEAR, 2015), and then adjust for the effects of dose uncertainty on the risk estimates. Nearly all studies have adjusted for potential confounding by sex, attained age and sometimes age at exposure. However, few studies have analyzed radiation risks with control for possible confounding by lifestyle (*e.g*., smoking), other disease risk factors or other sources of radiation exposure; these

factors may diminish the consistency of findings. Nevertheless, it should be emphasized that lifestyle or other disease risk factors will cause confounding only if their frequency (or intensity) varies appreciably according to dose. The most prominent lifestyle risk factor is smoking. Adjustment for socioeconomic status is used in several studies as an indirect approach for controlling for smoking and other lifestyle factors. Indirect approaches to examine the impact of smoking in several major studies have not found that smoking introduced substantial bias (Akiba, 2013; Davis *et al*., 2015; Hunter *et al*., 2013; Richardson *et al*., 2015). For a few studies, concomitant medical radiation exposures have been examined; for the Techa River study diagnostic medical exposures at the official clinic were included in the doses (Schonfeld *et al*., 2013). Other factors, such as losses to follow-up or incomplete disease ascertainment, would cause bias in the risk estimates only if they occur differentially according to dose levels. Few studies currently have biological samples to evaluate genetic or phenotypic biological factors that might cause effect modification of radiation risks.

Because individual studies with low doses (less than 100 mGy) almost inevitably have relatively low statistical power, the findings for radiation and solid cancer are often not statistically significant. Furthermore, studies may have sampling variation or confounding by other exposures (*e.g*., smoking or other lifestyle factors) which can diminish the consistency or validity of findings. Nevertheless, most large and high quality low- dose studies show positive risk coefficients (Shore *et al*., 2017), suggesting there may be cancer effects at low doses, which is consistent with, though not necessarily proving, the applicability of the LNT model for radiation protection. However, it should be recognized that, the risk of cancer at low doses is small.

The data regarding noncancer effects at low doses—cardiovascular diseases, cataracts, thyroid dysfunction, central nervous system effects—are mixed or null, suggesting at this time that an LNT assumption for radiation protection purposes for noncancer effects is not appropriate.

1.6 Overall Conclusions on the Use of the LNT Model

While the ongoing development of science requires a constant reassessment of prior and emerging evidence to assure that the approach to radiation protection is optimal, though not necessarily perfect, NCRP concludes that, based on current epidemiologic data, the LNT model (perhaps modified by a DDREF) should continue to be utilized for radiation protection purposes. This is in accord with judgment by other national and international scientific committees, based on somewhat older data than in the present report (ICRP, 2007; NA/NRC, 2006; UNSCEAR, 2008), that no alternative dose-response relationship appears more pragmatic or prudent for radiation protection purposes than the LNT model.

2. Introduction

2.1 Background

For over 40 y the linear nonthreshold (LNT) dose-response model has been used to develop practical and prudent guidance on ways to protect workers and the general public from the potential harmful effects of radiation while, at the same time, balancing the beneficial, justified, and optimized uses of radiation in our society. Indeed, in developing its basic radiation protection recommendations, as currently given in NCRP Report No. 116 (NCRP, 1993a), the Council reiterated its acceptance of the LNT for the dose-risk 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 increase linearly with dose. At higher doses, received acutely, such as in accidents, more complex (nonlinear) dose/risk relationships may apply" (NCRP, 1993a).

NCRP later reassessed the weight of scientific evidence for and against the LNT model without reference to associated policy implications in Report No. 136 (NCRP, 2001). As in previous reviews by the NCRP (1980; 1993c; 1997) the Council concluded that there was no conclusive evidence on which to reject the assumption of a LNT dose-response relationship for many of the risks attributable to low-level ionizing radiation (although it was acknowledged that additional data were needed) (NCRP, 1993b). The NCRP then noted that 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 ubiquitous low-LET background radiation (NCRP, 1987; 2015) is so small that it may never be possible to prove or disprove the validity of the LNT assumption at those dose levels.

The International Commission on Radiological Protection (ICRP) published a science evaluation report, Publication 99 (ICRP, 2005b), on low-dose extrapolation of radiation-related cancer risks and issued updated radiation protection recommendations based on the conclusion that "while existence of a low dose threshold does not seem unlikely for radiation- related cancers of certain tissues, and cannot be ruled out for all cancers as a group, the evidence as a whole does not favor the existence of a universal threshold, and there seems to be no particular reason to factor the possibility of a threshold into risk calculations for purposes of radiation protection (ICRP, 2007)." ICRP concluded that a LNT theory, combined with an uncertain DDREF for extrapolation of risk from high doses received acutely remains a prudent basis for radiation protection at low doses and low dose rates (ICRP, 2005b).

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576 The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) evaluates the
577 evidence of radiation-induced health effects from studies of the health of survivors of the atomic bombings of
578 Japan and of other exposed groups. It also reviews advances in understanding of the mechanisms by which
579 radiation-induced health effects can occur. These assessments provide the scientific foundation used by the
580 International Commission on Radiological Protection (ICRP) and other protection organizations in developing
581 their recommendations on radiation protection. UNSCEAR has concluded that the simplest representation of
582 tumorigenic response is a linear relationship, which is consistent with much of the available mechanistic and
583 quantitative data and strongly supports the scientific rationale for the LNT model as used in radiation protection
584 (UNSCEAR, 2000; 2006). A departure from linearity was noted for leukemia data, for which a linear-quadratic
585 function was used. It was noted that linear or linear-quadratic functions are used for representational purposes only
586 in evaluating possible radiation risks and that the actual response may involve multiple and competing processes
587 that cannot be separately distinguished.

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589 Based on the available epidemiologic data, UNSCEAR derived risk estimates and noted, as a first
590 approximation, linear extrapolation of the estimates at 1 Sv could be used for estimating solid cancer risks at lower
591 doses. The rationale was re-evaluated in the UNSCEAR 2006 Report, Effects of Ionizing Radiation Vol. 1
592 (UNSCEAR, 2008), that included several new cancer sites and used Bayesian methods for the incorporation of
593 dose uncertainty in the atomic-bomb survivor cohort risk, and concluded that "the data reviewed for its 2006
594 report do not necessitate changes in its current risk estimates for cancer and the hereditary effects of radiation."
595 However, this conclusion was based primarily on the LSS dose-response data following a high dose rate brief
596 exposure and not on an evaluation of cancer excesses after exposure at low dose rates.

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598 The National Academies (NA) published the Biological Effects of Ionizing Radiation (BEIR) VII report
599 (NA/NRC, 2006) that concluded that the available biological and biophysical data support a LNT risk model,
600 whereby the risk of cancer proceeds in a linear fashion at lower doses without a threshold. The U.S. Environmental
601 Protection Agency (EPA) in evaluating radiogenic risk models (EPA, 2011) noted that in general, results from
602 epidemiologic and radiobiologic research are consistent with an LNT dose-response model in which the risk of
603 inducing a cancer in an irradiated tissue by low doses of radiation is proportional to the dose to that tissue, while
604 acknowledging that new research might conceivably lead to revisions in the future. In contrast, a report from the
605 French Academy of Sciences (Tubiana *et al*., 2005) that focused primarily on radiobiology raised doubts about the
606 validity of using the LNT model for evaluating carcinogenic risks at low doses and suggested that since biological
607 mechanisms and responses appear different at low doses and high doses, an empirical relationship of linearity
608 validated at only doses >150 mSv may lead to an overestimation of risks at low doses.

Box (1979) concluded that "all models are wrong but some are useful". The LNT model is an assumption that has not been and likely cannot be scientifically validated in the low-dose range. Other dose-response relationships for the mutagenic and carcinogenic or detrimental effects of low-level radiation cannot be excluded, and there are notable exceptions to the LNT relationship seen in experimental and epidemiologic studies (Boice, 2015c; Dauer *et al*., 2010). Nonetheless, on the basis of the scientific knowledge to date the current judgment by national and international scientific committees is that no alternative dose-response relationship currently appears more pragmatic or prudent for radiation protection purposes than the LNT model.

2.2 LNT and the Estimation of Cancer Risk

As part of the process for developing nominal dose limits for radiation protection purposes, it is the current practice of ICRP, for example, to calculate total health detriment values for exposure to low doses and low dose rates of radiation (ICRP, 2007). Detriment values are based largely on the risk estimates for fatal cancers, nonfatal cancers and heritable effects (so-called stochastic effects) and also factors such as quality of life and adjustment for DDREF. Until recently, little consideration has been placed on noncancer effects (harmful tissue reactions, previously called deterministic effects) for the calculation of nominal risk, largely because it has been assumed that noncancer effects have quite large threshold responses and that cancer is dominant at low doses and low dose rates. This assumption is being reassessed, most specifically for cataracts and cardiovascular diseases (ICRP, 2012; NCRP, 2007). How to use this information, if indeed it is to be used, for noncancer responses in a detriment calculation remains a matter of scientific debate and clearly requires additional human data on radiation-induced adverse health outcomes.

The process of estimating risks for adverse health outcomes (cancer and noncancer) has relied almost exclusively on the available human epidemiology data from exposed populations, in particular the survivors of the atomic bombs in Japan, but with additional support from other exposed populations, including those exposed occupationally, environmentally, or from medical diagnostic and treatment procedures. Rather little use of the extensive radiobiology data has been made in the risk assessment process, with the exception of calculations of the DDREF and radiation weighting factors.

The general approach used by ICRP, EPA, NA/NRC (2006) and NCRP for cancer risk estimation used for protection purposes has been to develop a dose-response curve for all solid cancers assessed in the LSS following acute exposures that are highly influenced by the mid to high dose ranges and to extrapolate from this range to estimate cancer frequencies at low doses assuming no threshold, a LNT extrapolation. A DDREF is

applied to the slope of the linear extrapolation to estimate the cancer risk at low dose rates and often also for low doses. It is important to note that the use of an LNT extrapolation model is really a default approach because of a lack of definitive evidence to the contrary (Preston, 2003). Considerations of nonlinear extrapolations for solid cancer risk from high-to-moderate doses are continually being investigated and received some support from the recent studies on solid cancer incidence and mortality for the LSS (Grant *et al*., 2017; Ozasa *et al*., 2012).

A number of uncertainties are associated with the current approach to apply the scientific evidence for radiation protection, especially for DDREF and also with the model chosen for extrapolation (LNT) (NCRP, 2012). It is difficult to conduct epidemiology studies that will allow for direct measurement of adverse health outcomes at low doses and dose rates, although the ongoing Million Person Study (Boice, 2012a; 2017) can enhance the assessment at low doses and low dose rates. The way forward is most likely to include an integration of epidemiology and radiobiology data (NCRP, 2015).

2.3 Objective and Scope

This Commentary is to provide a review of recent data from new epidemiologic studies and data of populations exposed to radiation at low dose rates and to review the new data from the Life Span Study of atomic-bomb survivors. The purpose is to determine whether these epidemiologic studies broadly support the LNT model of carcinogenic risk as used in radiation protection or, on the contrary, whether there is sufficient evidence that the LNT model is inappropriate? The strength of support for the LNT model is evaluated for solid cancer incidence or mortality and secondarily for low dose-rate studies of leukemia. The focus is on new human studies on low doses and low dose rates. In addition, the report will briefly review current evidence regarding certain noncancer outcomes, such as cardiovascular diseases, and risk from childhood exposure and heritable radiation risk.

This Commentary was written by a committee of multi-disciplinary experts based on a comprehensive review of recent (within approximately 10 y) relevant epidemiologic studies, especially those that have been extensively studied, with attention paid to epidemiologic methodology, dosimetry and statistical approaches. The Committee performed a critical but balanced evaluation of these epidemiologic studies, including a description of their strengths and limitations, similar to the approach utilized in recent related reviews by UNSCEAR (2008; 2013). The present evaluation includes a detailed assessment of the dosimetric and statistical approaches employed for the epidemiologic study. The aim was to develop a perspective for each study and evaluate its strength with regard to radiation protection implications. Future directions and ongoing research needs were identified.