Strengths and Weaknesses of Dosimetry Used in Studies of Low-Dose Radiation Exposure and Cancer

Robert D. Daniels,

Division of Science Integration, National Institute for Occupational Safety and Health, Cincinnati, OH

Gerald M. Kendall,

Cancer Epidemiology Unit, NDPH, University of Oxford, Oxford, UK

Isabelle Thierry-Chef,

Barcelona Institute for Global Health, Barcelona, Catalonia, Spain

Universitat Pompeu Fabra, Barcelona, Catalonia, Spain

CIBER Epidemiología y Salud Pública, Madrid, Spain

Martha S. Linet,

Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD

Harry M. Cullings

Department of Statistics, Radiation Effects Research Foundation, Hiroshima, Japan

Abstract

Background: A monograph systematically evaluating recent evidence on the dose-response relationship between low-dose ionizing radiation exposure and cancer risk required a critical appraisal of dosimetry methods in 26 potentially informative studies.

Methods: The relevant literature included studies published in 2006–2017. Studies comprised case-control and cohort designs examining populations predominantly exposed to sparsely ionizing radiation, mostly from external sources, resulting in average doses of no more than 100 mGy. At least two dosimetrists reviewed each study and appraised the strengths and weaknesses of the dosimetry systems used, including assessment of sources and effects of dose estimation error. An overarching concern was whether dose error might cause the spurious appearance of a dose-response where none was present.

Results: The review included 8 environmental, 4 medical, and 14 occupational studies that varied in properties relative to evaluation criteria. Treatment of dose estimation error also varied

among studies, although few conducted a comprehensive evaluation. Six studies appeared to have known or suspected biases in dose estimates. The potential for these biases to cause a spurious dose-response association was constrained to three case-control studies that relied extensively on information gathered in interviews conducted after case ascertainment.

Conclusions: The potential for spurious dose-response associations from dose information appeared limited to case-control studies vulnerable to recall errors that may be differential by case status. Otherwise, risk estimates appeared reasonably free of a substantial bias from dose estimation error. Future studies would benefit from a comprehensive evaluation of dose estimation errors, including methods accounting for their potential effects on dose-response associations.

Ionizing radiation exposure is unavoidable in everyday life. The foremost concern about low-dose ionizing radiation exposure is the potential for increased risk of cancer (1). Since the 1950s, authoritative bodies have relied mostly on data from the Life Span Study (LSS) of Japanese atomic bomb survivors to project cancer risks from ionizing radiation exposure (2,3). The acute ionizing radiation exposure in the LSS population differs from the protracted lower dose rate exposures in most occupational and environmental settings; therefore, the transport of risk in the LSS to other populations (eg, radiation workers) is uncertain (4–6).

The direct estimation of risk is preferred when data are sufficient, and health risks from ionizing radiation in several populations have been studied extensively (2,3). In 2006, the National Research Council of the National Academy of Sciences' Committee on the Biological Effects of Ionizing Radiation (BEIR) published its most recent review of existing data on health effects from low levels of ionizing radiation, hereafter referred to as BEIR VII (2). The review examined a wide array of information from medically, occupationally, and environmentally exposed populations; however, the Committee again relied on LSS data to estimate risk because of uncertainty in risk estimates and a general lack of accounting for errors in dose estimation in other studies.

The relevant literature has grown considerably since BEIR VII. The National Cancer Institute is leading an effort by international experts to critically evaluate a group of post–BEIR VII studies and assess several potential sources of biases on estimates of risk from low-dose ionizing radiation exposure (7). The National Cancer Institute assessment largely followed recent guidance by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) for evaluating radiation epidemiologic studies (8). As a part of this assessment, the work herein is a systematic appraisal of the strengths and weaknesses of the dosimetry systems used in these studies, including an assessment of sources and effects of potential discrepancies between the true absorbed dose to target tissues from ionizing radiation (ie, the preferred dose quantity) and the value used in dose-response analyses, hereafter referred to as dose estimation error.

Methods

Study Selection

Details on study selection are provided elsewhere (7). Briefly, investigators systematically searched public domain databases for epidemiologic studies on radiation-exposed

populations published from 2006 through 2017. Studies were either cohort or case-control designs with dose-response analyses of the relationship between cumulative radiation dose and cancer, reporting effect measures in terms of risk per unit dose or at a given exposure level. The primary exposure was to sparsely ionizing radiation at low doses and low-dose rates resulting in an average absorbed dose to the whole-body or target tissue of interest of 100 mGy or less. Exposures stemmed mainly from external gamma and x-rays; however, contributions from other sources (eg, incorporated radionuclides or neutron exposures) were considered in some studies. Articles from the Fifteen-Country Workers Study (9) published within the eligible period were excluded because main findings were reviewed in BEIR VII (2). When more than one article pertained to a study population, the synthesis was limited to the study with the longest follow-up. When studies stemmed from the same population and observation period, selection was based on consensus of the monograph working group (7).

Assessment Strategy

Investigators categorized studies as environmental, occupational, or medical exposure. At least two dosimetrists independently reviewed each study within a category. All dosimetrists convened to discuss, reconcile, and consolidate disparate findings within a category to achieve consensus. Table 1 describes dose estimation errors considered in this review. Additional information is provided in Appendix A and a companion paper (27). Dose estimation error comprises both systematic and random components, where systematic error represents an inequality between the long-term averages of true [$X_{ij}(t)$] and observed [$Z_{ij}(t)$] dose to individual, i, in group, j, at time, t, and random errors represent natural variation in $X_{ij}(t)$ and $Z_{ij}(t)$. Measurement error [$U_{ij}(t)$] that is assumed to be independent and identically distributed is said to be unshared. Conversely, correlations in errors between individuals, groups, or time represent shared error. Random errors reduce statistical power (and increase the width of confidence intervals), but usually they do not distort the results of statistical tests of the null hypothesis. Systematic error that is nondifferential with respect to case status is unlikely to result in a spurious positive dose-response. In contrast, error that is differentially distributed can lead to false-positive or -negative results. The effect of a component of error on dose-response relationships depends on the magnitude and the error structure (eg, classical or Berkson) and whether it is shared among some participants or if independent (see Appendix A).

Each reviewer evaluated potential sources of dose estimation error (Table 1), strengths and weaknesses of the exposure assessment methods, and the potential for bias in risk estimates. Key issues evaluated were as follows:

- Directness: How were individual doses determined? Generally, greater weight is given to evidence from studies directly measuring dose at the individual level, followed by estimates derived from measurements on other similarly exposed individuals and then models using area measurements (eg, radionuclide plume or soil concentrations) and an individual's proximity to the radiation source (eg, work history, domicile).

- Complexity: Were exposures dynamic or occurring at a constant long-term average rate (as with natural background)? Did exposure scenarios involve

multiple radiation sources and pathways? In general, the likelihood of substantial dose estimation error increases with the complexity of the exposure scenario considered in the dose reconstruction.

- Completeness: Did investigators use complete data and consider all relevant sources and pathways? Systematic error can result from incomplete information on organ dose. To the extent practicable, reviewers assessed the completeness of the exposure database.

- Uncertainty: Was dose to the target organ or tissue assessed? To what degree was the potential for bias in dose estimates examined by investigators? Was there a known bias? Did investigators report dose estimates based on information that might have depended on the disease status of the individual (ie, potential for recall bias)? Did investigators account for dose error in dose-response analyses? The reviewers evaluated the investigators' efforts to examine the potential consequences of dose estimation errors on risk estimates.

- Validation: Reviewers assessed the extent to which investigators validated indirectly obtained dose estimates (eg, by direct measurements on a subsample population).

Results

Among numerous publications on radiation health effects since BEIR VII, 26 were selected for critical evaluation based on criteria used in the systematic review (7). The review included 8 environmental studies, 4 medical studies, and 14 occupational studies (Table 2). Among these, 11 (42%) reported organ absorbed dose (28,32,44,55,57,59,64,78,82,85,89). Others reported in units of equivalent or effective dose. Exposures spanned from 1905 to 2011, with 12 studies reporting exposures prior to 1960. The following sections briefly describe eligible studies and relevant findings. Table 3 summarizes key strengths and weaknesses of the dosimetry systems. Appendix B provides additional information on selected studies.

Environmental Studies

There were eight environmental studies (study IDs 1–8; Table 2). Data from individual monitoring were mostly unavailable; therefore, exposures were generally assessed using models relating source and pathway to an individual's potential for exposure. Exposure potential stemmed primarily from occupancy (ie, one's time and distance from the radiation source); however, some estimates included modifications given individual characteristics (eg, age, shielding, and food and water consumption). Environmental studies comprised exposure subcategories of natural background and human activities. The natural background studies (32,36,41,48) involved relatively constant rates of exposure from external sources (ie, single source and pathway), whereas human activities (28,29,44,49) involved planned and unplanned releases of radiation resulting in dynamic exposures to surrounding populations.

Information on dose estimation errors was sparse. Another potential weakness was the reliance on self-reported information in some environmental studies (28,29,32,44,49). Information obtained from interviews or questionnaires is subject to recall errors that could be differential by case status depending mostly on the timing of data collection. For example, the population-based case-control study of leukemia in children exposed from the Chernobyl accident (study ID 1) used information from interviews conducted after case ascertainment in estimating doses; however, investigators did not examine the potential for bias from differential recall (28).

Background Radiation Studies.—There were four natural background radiation studies (32,36,41,48). Three were national studies of the effects of terrestrial gamma rays that estimated dose using existing radiation survey data. Study investigators assessed dose without direct measurement or interview. In all three studies, exposures inside buildings contributed more dose compared with the outdoors. The Great Britain study (study ID 4) had access to individual measurements of gamma rays in buildings but assessed exposures to study subjects as the mean for the county district of birth (36). The Swiss and Finnish studies (IDs 5 and 7, respectively) aggregated results in the form of average outdoor gamma-ray dose rates in geographic grid squares (41,48). The Finnish study converted these to indoor dose rates using house-type specific shielding factors. The Great Britain study considered some sources of dose uncertainty (37) but concluded the effect from these sources was limited to a loss of statistical power. There was some evidence of a potential downward bias in risk estimates in the Swiss study possibly caused by a lack of dose information due to residential mobility (41). None of the national studies included dose from other radiation sources, such as ingestion of naturally occurring radionuclides and medical exposures; however, sensitivity analyses in the Finnish study found no evidence of a potential bias from unmeasured exposures related to computer tomography (CT) examinations. National study investigators did not evaluate other sources of dose uncertainty.

The Chinese background study (study ID 3) applied numerous measurements in the study and control areas to estimate indoor and outdoor doses based on hamlet-specific averages (32). Intercomparisons with groups of residents by dosimeters and biologic dosimetry systems provided some validation of dose estimates (33,108). One intercomparison study suggested that the average coefficient of variation (CV) of the ratio of measured values to the estimated values was less than 22% (33). The potential for confounding by medical exposures appears small based on previous studies of this cohort (109). Internal doses were not assessed. Dose error was not addressed in dose-response analyses.

Studies of Human Activities.—Human activity studies examined cancer risks in persons exposed to radioactive contamination in and around their place of residence (28,29,44,49). This group of studies required retrospective assessment of time-varying doses under different exposure scenarios. The levels of exposure were, in general, a function of source, occupancy, release rate, environmental transport, exposure pathway, and biokinetics. Given this complexity, the modeling necessary to estimate individual dose was unique to the scenario at hand, and the methods used were generally more complex than those for

background studies. A common weakness among these studies was the lack of accounting for dose estimation errors in dose-response analysis.

Study ID 1 is a population-based case-control study of childhood leukemia in regions of Belarus, Russia, and Ukraine contaminated by the Chernobyl accident (28). Davis et al. (28) calculated absorbed dose to red bone marrow (RBM) using residential histories and field measurements for external doses and radionuclide concentrations and assumptions on individual food and water consumption rates for internal doses. The dosimetry addressed time dependence of these parameters through residential changes of study subjects. The dose reconstruction used information on residence and personal information obtained by questionnaires administered after case ascertainment; however, there was no assessment of the potential for differential recall. Investigators used Monte Carlo simulation techniques and mean values of 1000 realizations from internal and external dose sources in dose-response analyses (personal communication with study authors on September 20, 2018). Excess risk was most evident in Ukraine, diminished in Belarus, and not found in Russia. Although investigators mentioned dosimetry errors as a possible cause, they deemed them an unlikely explanation for this heterogeneity because of the common dosimetry methods across countries. Instead, there was evidence of a bias in control selection such that Ukraine controls tended to be selected from less contaminated areas than cases given differences in selection procedures (110).

Study ID 2 examined cancer incidence from 1982 to 1995 among Caucasian adults (10 446 men and 11 048 women) who resided within 5 miles of the Three Mile Island (TMI) nuclear power station during the 1979 partial reactor core meltdown (29). Dose estimation combined self-reported information on occupancy within the 5-mile zone for 10 days following the accident with calculated time-dependent gamma dose-rate distributions (30). The approach intentionally overestimated doses (approximately 40%). Estimate precision was poor, with uncertainty in dose ranging from two- to sixfold. Dose-response analyses did not account for dose uncertainty. Because location data were collected about 2 months after exposure and well before follow-up, the potential for differential recall was small.

Study ID 6 examined cancer incidence in Techa River residents exposed to releases from the Russian Mayak Radiochemical Plant in the Southern Urals (44). Dose accrued externally from fission product contamination in river sediment and surrounding soil and accrued internally from the consumption of contaminated water, milk, and food. Interviews were used to assess group occupancy factors but not for individual dose assessment. Dose was treated as a time-dependent continuous variable calculated as the 5-year–lagged absorbed dose to the stomach. Doses were estimated using the Techa River Dosimetry System (TRDS-2009). As in most models, estimates relied on specific choices for uncertain modeling parameters, which is a source of shared uncertainty. Model validation efforts were noteworthy, including multiple intercomparisons with results from other models, radionuclide assays, and opportunistic dosimetry (45, 111–116). In particular, two studies of stable chromosome aberrations assayed via fluorescence in situ hybridization (FISH) suggest trends with dose a bit lower than (although comparable with) those in the Japanese atomic bomb survivors (115,116); these and various studies of electron paramagnetic resonance in tooth enamel have been summarized in a recent review (113). A recent

assessment yielded realization distributions with geometric standard deviation values for internal absorbed dose to the stomach of about 2 to 3, with external dose uncertainty slightly less (117). Other reports have indicated dose uncertainties on the order of four- to fivefold (108). Investigators did not account for dose uncertainty in dose-response analysis.

In the early 1980s, a large quantity of steel reinforcing bars contaminated with cobalt-60 was used in the construction of schools and residential buildings in Taiwan. This contamination was not discovered until 1992, when measurements revealed dose rates of 0.5–270 μGy/h (118). Breast cancer and leukemia were examined in a cohort of 6242 building residents with adequate information for dose assessment. As in previous studies of this cohort, doses were assessed using the Taiwan Cumulative Dose system (50,51). Occupancy factors were assessed by interviews, with some taking place after case ascertainment; therefore, some bias from differential recall appeared possible. Model validation procedures involved comparisons of radiation survey data and personal dosimetry measurements in a sample of residents. Dose-response analyses did not describe or account for dose estimation errors. Analysis of chromosome aberrations in these individuals has shown excess micronuclei (119), as well as dicentric chromosomes (120), in the exposed group, but no dose-response analyses were carried out in either study. Doses are likely too low to yield statistically significant trends, in view of the difficulty in detecting signals much below 100 mGy (121).

Medical Studies

The medical studies (study IDs 9 to 12; Table 2) included a variety of different populations and exposure scenarios: 1) Study ID 9 examined cancer in adult patients with acute myocardial infarction who underwent cardiac imaging and therapeutic procedures (52); 2) two studies (study IDs 10 and 11) focused on cancer risk following pediatric CT examinations (55,57); and 3) the Pooled International Radiation and Thyroid Cancer Epidemiology Study (PIRATES, study ID 12) is a pooled analysis of 12 studies of thyroid cancer following radiation exposure in childhood; subanalyses of nine studies focusing on children exposed to thyroid doses below 0.2Gy and 0.1Gy, respectively, satisfy criteria for this review (59). In PIRATES, cases with doses below 0.1Gy consisted mainly (82%) of atomic bomb survivors (122,123) and the Tinea Capitis cohorts (124); therefore, the present review focused on dose estimation errors in the Tinea Capitis cohort (60,61).

Dose estimation errors stemmed from missing data on both the patient's characteristics and the protocol implemented for every procedure, with, for example, age being used as a surrogate for physical characteristics such as height and weight. These errors are not likely to be differentially distributed. Medical radiologic examinations and/or treatments are usually carried out based on generic protocols developed for each procedure, which is then adapted to the physical characteristics of each patient. Missing information on the specific procedure used can be remedied by imputation of values based on typical protocols; however, this practice results in Berkson error and potentially shared systematic error. Moreover, organ doses are estimated using models based on measurements made with phantoms. Berkson error stems from using a single phantom for a range of body sizes. Shared error can result from an incorrect transport calculation for a given body size and orientation because of an imperfect phantom or transport code.

Cardiac Imaging Patients.—Eisenberg et al. (study ID 9) (52) examined cancer risks from radiation exposure in 82 861 adult patients undergoing fluoroscopically guided procedures (with or without contrast media) or nuclear medicine procedures following acute myocardial infarction. The authors calculated the cumulative effective dose for each patient by summing average values per procedure abstracted from the literature (53,54). This was accomplished by linking patient billing codes to procedures of interest, which were myocardial perfusion imaging (15.6 millisievert [mSv]), diagnostic cardiac catheterization (7.0 mSv), percutaneous coronary intervention (15.0 mSv), and cardiac resting ventriculography (7.8 mSv). These estimates did not consider heterogeneity in dose within broad groups of procedures or between centers or individuals. The investigators acknowledged that the variability of the doses between centers and operators was a limitation; however, they did not carry out a formal quantitative evaluation. Another limitation was the use of effective dose, which can greatly differ from the absorbed dose to organs of interest under partial-body irradiation and nuclear medicine procedures.

Pediatric CT Studies.—The French and United Kingdom CT cohorts (study IDs 10 and 11) were launched in the early 2000s and included 67 274 and 180 000 pediatric patients, respectively (55,57). These studies represent a new source; there were no previous CT studies in BEIR VII. In both studies, the authors collected information from the radiology information system of participating radiology departments. The radiology information system is devoted to the administrative recording of the radiology activities but includes only limited information on the type of examination performed (ie, body region scanned). Dose reconstruction therefore involved typical protocols defining image-acquisition parameters rather than individual data. Doses were based on typical values obtained at the national level in study ID 11 (58), whereas an extensive two-step survey in participating hospitals allowed hospital-based protocols to be used for dose reconstruction in study ID 10 (55,56), with imputation of median values from other radiology departments in cases of missing data. In both cases, assigned doses do not reflect interindividual variability. The Picture Archiving Communication System, which provides systematic recording and archiving of all images from the CT machine as well as a summary of the machine settings associated with each image taken, was progressively introduced worldwide after the mid1990s and could be used to derive more individualized organ dose estimates. Dose uncertainties were not quantified and therefore not considered in dose-response analysis.

The PIRATES (Low-Dose) Study.—The low-dose PIRATES study (study ID 12) examined thyroid cancer risk following exposure to low doses (<200 mGy) of ionizing radiation in childhood by pooling data from nine studies with individual estimates of thyroid dose (59). The Tinea Capitis cohort included 10 834 children treated in the 1950s in Israel, who represent most children involved in the pooled analysis (124). Individual doses used on-phantom measurements simulating x-ray prescriptions implemented in treatment centers (62). In reanalysis of the Tinea Capitis cohort, the authors assessed multiple sources of dose estimation error and developed a predictive model to account for major sources of uncertainty in dosimetry (60,61). The predictive model used information collected from three studies of anthropomorphic phantoms to estimate dose, using age at first irradiation, x-ray filtration, prescribed dosage, and the number of treatments. The model accounted for

missing data by averaging the prediction equation over the probability distribution of the required variables, given the available data. The model also accounted for random errors representing intraindividual effects (due to motion during the treatment or peculiarities in positioning of the body), interindividual effects (distribution of physical characteristics of the head), and other sources of random error. Researchers combined errors to compute the expected true dose from the available patient data and the prediction equation using a Monte Carlo approach. Thus, for dose-response modeling, Poisson regression calibration was accomplished by using expected true dose categorization.

Dose-response regression parameter estimates, standard errors, and inferences were essentially unchanged after accounting for measurement error, which study investigators attributed to the linearity of relative risk in dose and the predominance of Berksonian error (60,61). There was also little evidence of influence on the estimated potential effect modifiers attributable to dose uncertainty. This assessment accounted for most major sources of uncertainty; however, it did not account for measurement error associated with the phantom studies.

Occupational Studies

The 14 occupational studies (study IDs 13–26; Table 2) comprised three working populations: 1) Nuclear workers (NW) who were predominantly exposed to penetrating gamma rays with energies of 100–3000keV; 2) US radiologic technologists (USRT) exposed externally to x-rays with average energies of 30–50keV from diagnostic and therapeutic procedures; and 3) Chernobyl liquidators primarily exposed to high-energy gamma rays from fission product surface contamination resulting from the nuclear accident. Ten studies used measurement data from personal monitoring to estimate individual cumulative dose. Four studies combined incomplete measurement data with indirect methods using proxy measures, questionnaires, expert judgment, and statistical models. All studies updated information on cohorts (or subcohorts) previously reviewed in BEIR VII.

Nuclear Workers.—The NW studies (n=11; study IDs 13–26) comprised the largest group of occupational studies (Table 2). Study populations primarily comprised workers employed in research, weapons and fuel production, commercial power, or military operations. Doses encompassed exposures beginning as early as the mid-1940s and ending in 2005 (Table 2). Annual exposure patterns largely follow Cold War weapons production, with the bulk of the collective dose in studies occurring in the mid-1960s (Appendix B). There was overlap between studies stemming from the United Kingdom, United States, and French NW studies (66,81,95) comprising subcohorts pooled in the International Nuclear Workers Study (INWORKS) (82). Also, some Korean workers in a cancer incidence study (study ID 16) (68) were included in a previous mortality study (study ID 13) (63).

INWORKS (study ID 23) examined mortality patterns among 308 297 nuclear workers employed in France, the United Kingdom, and the United States between the years 1944 and 2005 (82,83,125,126). This study updated the dosimetry system used in the previous collaborative study coordinated by the International Agency for Research on Cancer, which included a comprehensive assessment of dose uncertainties (84). Investigators made

considerable efforts to acquire complete dose histories and to derive unbiased estimates of absorbed dose to target tissues, considering known sources of systematic errors in facility dosimetry over time (17,84). In particular, investigators derived facility- and time-specific "bias factors" to estimate absorbed dose from recorded dose. For RBM dose, recorded values were divided by bias factors ranging from 1.4 to 2.2, with corresponding CV values ranging between 0.2 and 0.6. For colon dose, which was used in analyses of all solid cancers combined, factors ranged from 1.2 to 2.1 (CV values 0.3–0.8). Investigators also quantified uncertainty in dose conversion; however, dose-response analyses did not use this information.

INWORKS comprised several subpopulations in previous epidemiologic investigations spanning decades. Over the course of these studies, there have been a number of improvements in dose estimates afforded through multiple records reviews. The extended follow-up also enabled dosimetry to incorporate improvements in measurements over time; however, this did not alleviate errors in early dosimetry that were carried forward. By design, the selection of similar study populations reduced heterogeneity and the potential confounding from unmeasured high linear energy transfer radiations and incorporated radionuclides. Nevertheless, data were inadequate to quantify contributions from internal dose and neutron exposures. Instead, dose-response analyses indirectly examined effects from other radiations in alternative models (82,83).

INWORKS and the US atomic veterans study (study ID 24) estimated absorbed dose (82,85), whereas others used unadjusted doses in units of whole-body equivalent dose (66,69,74), personal dose equivalent at a tissue depth of 10mm [H_p(10)] (81,95) or effective dose (63,68,71,80). Most data originated from measurements using film meters in the early years (1940s–1980s) and thermoluminescent dosimeters thereafter. The US atomic veterans study also used available measurement data from film meters; however, relatively few individuals were assigned personal dosimetry (85). Only 25% of participants had film badge records accounting for at least 80% of their dose (86). Therefore, estimates of RBM-absorbed dose stemmed primarily from group radiation measurements or by using time-motion models based on job descriptions and area radiation levels. There was no information on validation methods, although there was reasonable agreement with estimates from a detailed dose reconstruction involving a subset of workers (86). The average CV in the subset analysis was about 0.4–0.5, and values ranged upward of threefold in some exposure scenarios. In this comparison, doses were consistently lower in the detailed dose reconstruction compared with the cohort-assigned values; therefore, a scaling factor of 0.64 was used in the epidemiologic study to correct cohort doses (85).

Some NW populations were susceptible to dose from incorporated radionuclides and neutron exposures (Table 4). Recorded whole-body doses included contributions from neutrons (63,66,68,69,71,80) and 50-year committed effective doses from incorporated radionuclides (63,68,71,80) in several studies. The Rocketdyne NW study (study ID 17) quantified internal dose from 16 different radionuclides; however, quantification was limited to those workers judged to have a 50-year committed effective dose of 10 mSv or greater (69,70). In that study, there were 46 970 cohort members, including 5801 monitored for radiation and 2322 monitored for internal dose. Study investigators estimated annual doses

from internally deposited radionuclides for 292 workers. The inclusion of internal dose showed no meaningful effects on the dose-response. The Canadian and US NW studies (IDs 19 and 22, respectively) estimated dose from tritium uptakes (74,81). Dose-response analyses conducted with and without tritium dose or treating tritium as a separate model term did not suggest substantial tritium-related effects. In the French NW study (study ID 26), investigators examined confounding by internal exposures and concluded that neglecting internal dose did not substantially bias risk estimates in this cohort (104). Studies without adequate quantitative data on neutron exposures or incorporated radionuclides examined the effects in various sensitivity analyses using markers of exposure potential (66,82,95). These analyses did not reveal evidence of a strong bias in risk estimates resulting from excluding dose from neutrons and internal emitters.

Doses below detection limits (BDL) were explicitly addressed only in the UK National Registry for Radiation Workers (UKNRRW) study (study ID 15) (66); however, three other studies (study IDs 22, 23, and 26) used dosimetry systems that have addressed detection limits in previous reports involving full and subcohort populations (22,23,25,67,106,127,128). In studies of the UKNRRW study, results with and without BDL dose adjustments revealed no evidence of meaningful bias in risk estimates (67,129). Similarly, there was little evidence of a strong bias from BDL doses in other studies (22,23,127,128). Among these, a "worst-case" example found a 22% drop in the linear excess relative risk per sievert (ERR/Sv) for all cancers in a previous study of Oak Ridge National Laboratory workers, also included in the US NW study and INWORKS, after adjusting for BDL doses between 1943 and 1956, when film badge dosimeters were processed weekly (128). In subsequent examinations of these data, effects on risk estimates were more modest and potentially completely offset by other errors (22,127).

At some facilities, notional doses were assigned to periods of unmonitored exposure (eg, because of a lost badge or doses at a previous facility) as a means of assuring compliance with dose limits. The UKNRRW study accounted for notional doses, which lowered the collective dose from pro-rata assignments from 295 person-Sv to 15 person-Sv but did not meaningfully change risk estimates given a small change in the total collective dose (4260 person-Sv) (25). The lack of substantial bias from notional doses was also evident in a study of shipyard workers included in the US NW study and INWORKS (26).

Most studies expended considerable efforts to gain complete exposure histories; nevertheless, investigators of the Canadian NW study raised concern over missing data (74). The study may have omitted exposures to a group of early workers because of information lost during transfer to the central dose registry. The authors speculated that the missing data might explain the dose-related risk of solid cancer mortality observed among these workers that was absent among other workers; however, there was no attempt to examine the plausibility of the error to fully explain the risk difference. Recently, the missing data have been found and researchers have initiated an update to the study; therefore, lingering questions on bias in risk estimates from the missing data may be resolved soon (personal communication with study authors on October 17, 2018).

Work-related medical x-ray examinations (WRX) are a potential source of unmeasured occupational exposure in some cohorts. The majority of WRX dose stems from fluoroscopic or photofluorographic chest exams in the 1940s and 1950s; therefore, studies including workers employed prior to 1960 appear more susceptible to dose error from this source (130–133). In some US NW studies, WRX data were abstracted from medical records to estimate dose (101–103,134–137). Of these, three examined the potential for bias from unmeasured WRX, with two reporting no effect (134,135) and one showing attenuation of the association between lung cancer mortality and external dose, including WRX (136). In this review, WRX was examined in the French NW cohort (105). Medical records were unavailable; therefore, doses were estimated as the product of assumed yearly exams and dose per procedure. Because it could not be ruled out, fluoroscopy (1.5–3.0 mSv per exam) was assumed prior to 1955 and radiography (0.1–0.3 mSv per exam) thereon. Risk estimates without WRX were imprecise in this cohort; adding WRX doses led to modest attenuation (7–47%) and further reduction in precision, yet positive but nonsignificant dose-response associations persisted.

The NW studies did not account for random measurement error in dose-response analyses; however, doses that are the sum of many measurements (ie, as in cumulative dose) likely have relatively small random error. Previous examinations have provided little evidence of a substantive bias from random error. Xue et al. (127) examined the simultaneous effects of BDL doses and random error on findings in a study of Oak Ridge National Laboratory workers included in the US NW study and INWORKS. They concluded that random errors in measurements were unlikely to substantially bias risk estimates. Similarly, a detailed examination of the relative error in cumulative doses from film badges worn by Hanford workers (also included in study IDs 22 and 23) suggested that the increase in the total variance of measured cumulative doses is unlikely to be more than 1% of the total variance in true cumulative doses, leading to negligible bias in the risk estimates (138). A similar conclusion was reached regarding the Canadian NW study (75).

US Radiologic Technologists.—Three publications on cancer in the USRT (study ID 25) were eligible for consideration (89–91), with each using identical dosimetry but differing target organs of interest (92). For brevity, the narrative is limited to a study of breast cancer incidence and mortality patterns in females certified by the American Registry of Radiologic Technologists for at least 2 years from 1926 through 1982 (89). Exposures were reconstructed for the period 1916–1997 for technologists conducting medical diagnostic and therapeutic procedures using ionizing radiation. The mean cumulative breast dose was 37 mGy, ranging from 0.058 to 2500 mGy. (92).

Investigators used available personal dosimetry measurements and information on work procedures, protection practices (eg, apron use), x-ray imaging technology, and other factors to estimate whole-body dose equivalent and subsequently absorbed dose to breast tissue. Parameters used in estimation procedures were treated as expected values with an associated probability distribution. Monte Carlo methods were used to generate multiple dose realizations for the full cohort. These methods accounted for sources of shared and unshared errors, including treatment of BDL doses and errors associated with changing dosimetry and work practices over time. Regression calibration was used to account for random error. The

CV in cumulative breast dose from 1000 dose realizations was about 2.4. The dosimetry system was partly validated by comparison with badge reading at five major US hospitals and biodosimetry methods linking this study to observations in LSS participants (92). Validation was also conducted by a study of stable chromosome aberrations assayed in 238 of the USRT participants using FISH suggesting that the trends of stable chromosome aberrations with dose are comparable with those in the Japanese atomic bomb survivors and in various other groups (139).

Dosimetry strengths were the collection and integration of individual film badge dose data available between the years 1960 and 1997, extensive efforts to account for sources of dose estimation error, and methods used to validate dose estimates. However, relying on indirect estimation because of the unavailability of measurement data prior to 1960 was an important limitation. Film badge measurements were available for 39% of the years worked, with about 25% of the collective dose derived from film badge data. The proportion of film badge–based dose estimates varied by the year of first exposure, ranging from essentially none for the earliest workers to 60% for those who began working after 1980. Moreover, birth cohort and total cumulative dose were associated, and the dose-related excess risk of breast cancer incidence was strongest in women born before 1930 (ERR/Gy = 1.6, 95% confidence interval [CI] = 0.3 to 3.9). In fact, the experience of early workers was the primary determinant of cancer incidence and mortality risk. Because of the large uncertainty in early doses and the strong birth cohort effect, the authors interpreted results cautiously.

Chernobyl Liquidators.—Two case-control studies were reviewed. The first (study ID 14) was nested within cohorts of mostly male (>95%) liquidators from Belarus, Russia, and Baltic countries who took part in recovery activities between the accident date (April 26, 1986) and December 31, 1987 (64). The second (study ID 20) was nested within a cohort of 110 645 male Ukrainian workers who were 20 to 60years of age during cleanup activities between the years 1986 and 1990 (78). The exposure to liquidators was predominantly penetrating whole-body gamma radiation emitted from radionuclides (primarily ^{137}Cs) on contaminated surfaces. Dose from ingesting contaminated food and drinking water was plausible, especially in those living in Belarus; however, investigators posited that the dose contribution from incorporated radionuclides was at least an order of magnitude lower than the external contribution (140).

Studies of Chernobyl liquidators reported in BEIR VII relied primarily on dose data in the Russian National Medical and Dosimetric Registry, which was known to have several gaps and problems (79,140). To account for the Russian National Medical and Dosimetric Registry shortcomings, researchers combined information from available radiation measurements with self-reported data to develop the Radiation Dose Reconstruction with Uncertainty Estimates (RADRUE) software package used to estimate absorbed dose to RBM for workers in both studies. In general, RADRUE dose estimates are the product of exposure rate and irradiation time, given a number of exposure scenario parameters. Input data included work histories, exposure rates, adjustment factors for protective equipment used, and dose conversion coefficients. The output included point estimates of dose and associated uncertainties, the latter reported as geometric standard deviation values across all liquidator categories between 1.7 and 3.4 (65). The methods used to estimate uncertainty enabled

examination of the effects of random errors on dose-response analyses, which suggested negligible effects on risk estimates, although confidence intervals were slightly wider (64). Validation of RADRUE was accomplished by intercomparisons with data from personal dosimeters and biological dosimetry, including both ESR and FISH (64,65,79,141). RADRUE does not provide information on internal exposure; however, separate estimation of doses and attendant uncertainties from consumption of contaminated food were calculated for study participants who resided in Belarus.

The dosimetry systems relied on self-reported information from a selected set of cases and controls, using in-person and proxy interviews. As a result, differential recall may have introduced a bias in dose estimates. To reduce potential biases, the interviewers were blinded to disease status. Similarly, dosimetrists estimated doses without knowledge of disease status. Some efforts to assess recall accuracy in these workers have suggested that a large bias in dose estimates was unlikely; however, an examination sufficient to exclude a bias in liquidator doses is difficult, if not impractical (79). Thus, the potential for spurious dose-response results from differential recall cannot be ruled out.

Discussion

It has been more than a decade since the BEIR VII review. An important conclusion in BEIR VII was that low-dose studies were generally unsuitable for projecting population risks, in part, because dose estimation errors had not been taken into account. Since then, there have been nearly 100 publications of study findings on the dose-response association between low linear energy transfer ionizing radiation and cancer. Among these, 26 studies meeting a priori quality for selection were independently reviewed by at least two dosimetrists against common key characteristics of directness, complexity, completeness, uncertainty, and validation of dosimetry methods. This approach provided a far-reaching review and consistent presentation of findings by source of exposure. The findings, in concert with ongoing analyses of other factors potentially affecting risk estimates, enable a comprehensive assessment of the weightof-evidence on low-dose radiation carcinogenicity. Of studies evaluated, three case-control studies vulnerable to differential recall appeared most susceptible to a spurious dose-response caused by dose error (28,64,78). These and other sources of dosimetry error in study categories of environmental, medical, and occupational exposures are described below.

Environmental Studies

Most environmental studies in BEIR VII were ecologic, including all background radiation studies and previous studies of TMI residents. Excluding children of exposed adults, 17 longitudinal studies were reviewed in BEIR VII; therefore; the eight eligible studies herein represent a noteworthy increase in available literature. There were earlier examinations of Techa River– and Chernobyl-exposed residents that preceded the studies in the current review (28,44). In particular, the Techa River dose reconstruction has evolved considerably post–BEIR VII, including some validation. In contrast, there was no indication of improvements in dose reconstruction supporting Chernobyl resident studies.

Except for study ID 2 (29), environmental studies were reviewed by UNSCEAR (108). In its 2017 report to the General Assembly, UNSCEAR found that risk estimates from these studies were generally consistent with a range of risk estimates found in other studies. Environmental studies are potentially informative on radiation risks at very low doses, although the detection of small effects is demanding in terms of study power and the potential for residual confounding. As with any source, dosimetric biases might be more influential on risk estimates in studies of very low doses, such as the national background radiation studies; however, there was no evidence of substantial dosimetric bias in these studies. Nevertheless, the environmental studies generally provided limited information on dose uncertainty, because dose errors were not accounted for in dose-response analyses.

Medical Studies

Among medical studies, CT studies (study IDs 10 and 11) appear most informative given similar methods used between studies and a lack of comparable studies in BEIR VII. Investigators made substantial efforts to estimate CT patient organ doses from hundreds of protocols. The dosimetry systems made use of data from radiation on-phantom measurements related to generic protocols developed for each procedure. Using group-averaged estimates resulted in Berkson error that is unlikely to bias risk estimates markedly. Shared errors were possible; however, these errors were likely to be independent of case status. Future improvements in dose estimates can be achieved with CT parameters on individual patients. Among other study limitations related to dosimetry, analyses did not consider dose from other diagnostic examinations or from CTs in nonparticipating hospitals, although these doses were likely to be small in comparison. Furthermore, assessments of dose uncertainty and subsequent treatment in dose-response analyses were lacking.

Occupational Studies

BEIR VII identified 25 studies of nuclear industry workers (principal studies listed in table 8–2, US Atomic Veterans described on page 212, and Appendix E of BEIR VII) published between the years 1981 and 2005 (2). The 11 studies herein represent notable additions to NW literature, including updates to studies in BEIR VII. Most studies relied on personal measurements, which BEIR VII and the present investigators recognize as the most complete and informative source for studying the relationship between low-dose protracted ionizing radiation exposure and cancer (2). Improvements in dosimetry included expanded searches for dose data for some populations (17,69,74,81) and added information on more recent exposures (17,63,66,68,69,71,74,80,81,95). Other improvements included detailed assessments of dose estimation errors, which can inform on estimates of absorbed dose. In particular, INWORKS improved on dosimetry methods in the previous International Agency for Research on Cancer studies (9,142) to account for systematic errors related to radiation fields, dosimetry practices, and dosimeter technology (17). INWORKS methods were also used in the French NW study (95). Nevertheless, dose estimation errors were unavoidable, especially during the early years when contributions to individual dose from BDL doses, neutrons, and WRX could be substantial. The potential effects on the dose-response from these sources remain unclear.

BEIR VII included studies of radiation-exposed medical and dental workers, including the USRT cohort; however, these studies generally lacked dose estimates suitable for dose-response analyses. In recent USRT studies, improvements in dosimetry have provided dose estimates with attendant uncertainties for dose-response modeling (89,90). The USRT cohort is among the first to use Monte Carlo computer simulation techniques to quantify and account for sources of shared and unshared errors in an occupational cohort, including missed dose and errors associated with changing dosimetry practices over time. A similar approach was taken in the Chernobyl liquidator studies (64,78). BEIR VII concluded that risk estimates in studies available at that time were unreliable because of a lack of validated individual dose estimates (2). Since then, there has been marked improvement in dosimetry with the development and implementation of RADRUE, which has been used in several studies published since BEIR VII (64,78,143,144).

This review assessed the quality of dosimetry systems in 26 studies published since BEIR VII, which collectively represent a sizeable addition to the literature on low-dose radiation exposure and cancer. Nearly all studies provided reasonable assurances that risk estimates were free of a substantial bias from dose-estimation errors; however, few sources of error were thoroughly explored. In this review, a known or suspected bias in dose estimates was found in six studies:

- The study of TMI residents (study ID 2) in which doses were intentionally overestimated for protection purposes (29)

- The Canadian NW study (study ID 19), where authors speculated that missing doses among a group of early workers may explain the observed positive dose-response for solid cancer in these workers (74)

- The case-control studies of Chernobyl liquidators (study IDs 14 and 20) and residents (study ID 1) because of the potential for differential recall from questionnaires administered after case ascertainment (28,64,78)

- The USRT breast cancer study (study ID 25), where greater excess risk per unit of dose was seen in early workers (when dose levels were highest and dose uncertainty greatest) and the effects of birth cohort and dose uncertainty on risk estimates could not be disentangled. As such, the authors cautioned interpretation of findings because of possible systematic errors in early doses that were not fully accounted for in dose reconstruction (89).

Information on recall in the Chernobyl case-control studies was inadequate to completely rule out recall errors in dose that may be differential by case status (28,64,78). Additional examination of the potential for recall bias is warranted. Only study ID 2 reported a known bias, which would not result in spurious excess risk. The effects from incomplete exposure data in the Canadian NW Study remain unclear. Thus, until inclusion of the newly found dosimetry data in dose-response analysis, interpretation should be limited to estimates from the cohort excluding early workers suspected of incomplete dose histories. The potential bias in early doses among USRT workers is likely to be nondifferential; therefore, this error is unlikely to fully explain the heterogeneity in risk by birth cohort.

Overall, this assessment did not reveal strong evidence of spurious dose-response associations stemming from dose error in the studies reviewed. Advancements in dosimetry systems used in epidemiologic studies since BEIR VII are evident; nevertheless, there are areas for further improvement. In particular, future studies would benefit from a more comprehensive evaluation of systematic and random dosimetric errors, including the development and use of methods accounting for their potential effects on dose-response associations.

Acknowledgments

References

1. International Agency for Research on Cancer (IARC). Radiation, Volume 100D, a review of human carcinogens In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: IARC; 2012;.

2. National Research Council. Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2. Washington DC: National Academies Press; 2006.

3. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Effects of ionizing radiation, Annex A: epidemiological studies of radiation and cancer In: UNSCEAR 2006 Report to the General Assembly, with Scientific Annexes. New York, NY: UNSCEAR; 2008.

4. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Uncertainties in risk estimates for radiation-induced cancer, Annex B In: UNSCEAR 2012 Report to the General Assembly with Scientific Annexes. Sources, Effects and Risks of Ionizing Radiation. New York, NY: UNSCEAR; 2015.

5. Wakeford R Radiation effects: modulating factors and risk assessment - an overview. Ann ICRP. 2012;41(3–4):98–107. [PubMed: 23089008]

6. National Council on Radiation Protection and Measurements (NCRP). Implications of Recent Epidemiologic Studies for the Linear-Nonthreshold Model and Radiation Protection. Bethesda, MD: NCRP; 2018.

7. Berrington de Gonzalez A, Daniels RD, Cardis E, et al. Epidemiological studies of the low-dose ionizing radiation and cancer: rationale for the monograph and overview of the eligible studies. JNCI Monographs. 2020;2020(56): 97–113.

8. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Principles and criteria for ensuring the quality of the committee's review of epidemiological studies of radiation exposure, Annex A In: UNSCEAR 2017 Report to the General Assembly with Scientific Annexes. Sources, Effects and Risks of Ionizing Radiation. New York, NY: UNSCEAR; 2018.

9. Cardis E, Vrijheid M, Blettner M, et al. Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. BMJ. 2005; 331(7508):77. [PubMed: 15987704]

10. Gilbert ES. The impact of dosimetry uncertainties on dose-response analyses. Health Phys. 2009;97(5):487–492. [PubMed: 19820458]

11. Schafer DW, Gilbert ES. Some statistical implications of dose uncertainty in radiation dose-response analyses. Radiat Res. 2006;166(1):303–312. [PubMed: 16808615]

12. Bateson TF, Wright JM. Regression calibration for classical exposure measurement error in environmental epidemiology studies using multiple local surrogate exposures. Am J Epidemiol. 2010;172(3):344–352. [PubMed: 20573838]

13. Greenland S, Gustafson P. Accounting for independent nondifferential misclassification does not increase certainty that an observed association is in the correct direction. Am J Epidemiol. 2006;164(1):63–68. [PubMed: 16641307]

14. Dosemeci M, Wacholder S, Lubin JH. Does nondifferential misclassification of exposure always bias a true effect toward the null value? Am J Epidemiol. 1990;132(4):746–748. [PubMed: 2403115]

15. Wacholder S When measurement errors correlate with truth: surprising effects of nondifferential misclassification. Epidemiology. 1995;6(2):157–161. [PubMed: 7742402]

16. National Council on Radiation Protection and Measurements (NCRP). Radiation Dose Reconstruction: Principles and Practices. Bethesda, MD: NCRP; 2010 NCRP Report No. 163.

17. Thierry-Chef I, Richardson DB, Daniels RD, et al. Dose estimation for a study of nuclear workers in France, the United Kingdom and the United States of America: methods for the International Nuclear Workers Study (INWORKS). Radiat Res. 2015;183(6):632–642. [PubMed: 26010707]

18. Daniels RD, Schubauer-Berigan MK. Bias and uncertainty of penetrating photon dose measured by film dosemeters in an epidemiological study of US nuclear workers. Radiat Prot Dosimetry. 2005;113(3):275–289. [PubMed: 15769802]

19. Gilbert ES, Fix JJ, Baumgartner WV. An approach to evaluating bias and uncertainty in estimates of external dose obtained from personal dosimeters. Health Phys. 1996;70(3):336–345. [PubMed: 8609025]

20. Gilbert ES, Thierry-Chef I, Cardis E, et al. External dose estimation for nuclear worker studies. Radiat Res. 2006;166(1):168–173. [PubMed: 16808605]

21. Richardson DB, Ciampi A. Effects of exposure measurement error when an exposure variable is constrained by a lower limit. Am J Epidemiol. 2003;157(4): 355–363. [PubMed: 12578806]

22. Xue X, Shore RE, Ye X, et al. Estimating the dose response relationship for occupational radiation exposure measured with minimum detection level. Health Phys. 2004;87(4):397–404. [PubMed: 15359186]

23. Inskip H, Beral V, Fraser P, et al. Further assessment of the effects of occupational radiation exposure in the United Kingdom Atomic Energy Authority mortality study. Br J Ind Med. 1987;44(3):149–160. [PubMed: 3828241]

24. Daniels RD, Yiin JH. A comparison of statistical methods for estimation of less than detectable ionising radiation exposures. Radiat Prot Dosimetry. 2006;121(3):240–251. [PubMed: 16517566]

25. Muirhead CR, Goodall AA, Haylock RG, E., et al. Second Analysis of the National Registry for Radiation Workers, Occupational Exposure to Ionizing Radiation and Mortality. Chilton, Didcot, Oxfordshire, UK: National Radiological Protection Board (NRPB); 1999 Report NRBP-R307.

26. Daniels RD, Taulbee TD, Chen P. Radiation exposure assessment for Portsmouth Naval Shipyard health studies. Radiat Prot Dosimetry. 2004; 111(2):139–150. [PubMed: 15266069]

27. Gilbert ES, Little MP, Preston DL, et al. Interpretation of epidemiologic studies of populations exposed to low-dose, high-energy photon radiation. JNCI Monographs. 2020;2020(56):176–187.

28. Davis S, Day RW, Kopecky KJ, et al. Childhood leukaemia in Belarus, Russia, and Ukraine following the Chernobyl power station accident: results from an international collaborative population-based case-control study. Int J Epidemiol. 2006;35(2):386–396. [PubMed: 16269548]

29. Han YY, Youk AO, Sasser H, et al. Cancer incidence among residents of the Three Mile Island accident area: 1982–1995. Environ Res. 2011;111(8): 1230–1235. [PubMed: 21855866]

30. Gur D, Good WF, Tokuhata GK, et al. Radiation dose assignment to individuals residing near the Three Mile Island nuclear station. Proc PA Acad Sci. 1983;57(1):99–102.

31. Woodard K Assessment of Offsite Radiation Doses from the Three Mile Island Unit 2 Accident. Middletown, PA: Pickard, Lowe, and Garrick, Inc.; 1979 Report No. TDR-TMI-116.

32. Tao Z, Akiba S, Zha Y, et al. Cancer and non-cancer mortality among inhabitants in the high background radiation area of Yangjiang, China (1979–1998). Health Phys. 2012;102(2):173–181. [PubMed: 22217590]

33. Morishima H, Koga T, Tatsumi K, et al. Dose measurement, its distribution and individual external dose assessments of inhabitants in the high background radiation areas in China. J Radiat Res. 2000;41(suppl): 9–23.

34. Yuan YL, Morishima H, Shen H, et al. Recent advances in dosimetry investigation in the high background radiation area in Yangjiang, China In: Wei L, Sugahara T, Tao Z, eds. High Levels of Natural Radiation 1996: Radiation Dose and Health Effects. Amsterdam: Elsevier; 1997:223–233.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

35. Yuan Y, Shen H, Sun Q, et al. Estimation of individual doses from external exposures and dose-group classification of cohort members in high background radiation area in Yangjiang, China. Chin J Radiol Med Prot. 1999;19(2): 99–103.

36. Kendall GM, Little MP, Wakeford R, et al. A record-based case-control study of natural background radiation and the incidence of childhood leukaemia and other cancers in Great Britain during 1980–2006. Leukemia. 2013;27(1): 3–9. [PubMed: 22766784]

37. Kendall GM, Wakeford R, Athanson M, et al. Levels of naturally occurring gamma radiation measured in British homes and their prediction in particular residences. Radiat Environ Biophys. 2016;55(1):103–124. [PubMed: 26880257]

38. Kendall GM, Hughes JS, Oatway WB, et al. Variations in radiation exposures of adults and children in the UK. J Radiol Prot. 2006;26(3):257–276. [PubMed: 16926469]

39. Kendall GM, Fell TP, Harrison JD. Dose to red bone marrow of infants, children and adults from radiation of natural origin. J Radiol Prot. 2009;29(2): 123–138. [PubMed: 19454799]

40. Kendall GM, Bunch KJ, Miles J, et al. Report of a Record-Based Case-Control Study of Natural Background Radiation and Incidence of Childhood Cancer in Great Britain. Chilton, Didcot, UK: Health Protection Agency (HPA); 2013 Report No. HPA-CRCE-045.

41. Spycher BD, Lupatsch JE, Zwahlen M, et al. Background ionizing radiation and the risk of childhood cancer: a census-based nationwide cohort study. Environ Health Perspect. 2015;123(6):622–628. [PubMed: 25707026]

42. Rybach L, Bachler D, Bucher B, et al. Radiation doses of Swiss population from external sources. J Environ Radioact. 2002;62(3):277–286. [PubMed: 12164632]

43. International Atomic Energy Agency (IAEA). Uranium Exploration Data and Techniques Applied to the Preparation of Radioelement Maps. Vienna, Austria: IAEA; 1997 IAEA-TECDOC-980.

44. Davis FG, Krestinina LY, Preston D, et al. Solid cancer incidence in the Techa River incidence cohort: 1956–2007. Radiat Res. 2015;184(1):56–65. [PubMed: 26121228]

45. Degteva MO, Kozheurov VP, Tolstykh EI, et al. The Techa River dosimetry system: methods for the reconstruction of internal dose. Health Phys. 2000; 79(1):24–35. [PubMed: 10855775]

46. Degteva MO, Kozheurov VP, Burmistrov DS, et al. An approach to dose reconstruction for the Urals population. Health Phys. 1996;71(1):71–76. [PubMed: 8655333]

47. Degteva MO, Shagina NB, Tolstykh EI, et al. Individual Dose Calculations with Use of the Revised Techa River Dosimetry System TRDS-2009D: Final Report for Milestone 22. Springfield, VA: National Technical Information Service; 2009 Pacific Northwest National Laboratory (PNNL) Report No. PNNL-18915.

48. Nikkila A, Erme S, Arvela H, et al. Background radiation and childhood leukemia: a nationwide register-based case-control study. Int J Cancer. 2016; 139(9):1975–1982. [PubMed: 27405274]

49. Hsieh WH, Lin IF, Ho JC, et al. 30 years follow-up and increased risks of breast cancer and leukaemia after long-term low-dose-rate radiation exposure. Br J Cancer. 2017;117(12):1883–1887. [PubMed: 28972968]

50. Cardarelli J 2nd, Elliott L, Hornung R, et al. Proposed model for estimating dose to inhabitants of 60Co contaminated buildings. Health Phys. 1997;72(3): 351–360. [PubMed: 9030836]

51. Hwang JS, Chan CC, Wang JD, et al. Radiation exposure modeling for apartment living spaces with multiple radioactive sources. Health Phys. 1998; 74(3):379–386. [PubMed: 9482604]

52. Eisenberg MJ, Afilalo J, Lawler PR, et al. Cancer risk related to low-dose ionizing radiation from cardiac imaging in patients after acute myocardial infarction. CMAJ. 2011;183(4):430–436. [PubMed: 21324846]

53. Fazel R, Krumholz HM, Wang Y, et al. Exposure to low-dose ionizing radiation from medical imaging procedures. N Engl J Med. 2009;361(9):849–857. [PubMed: 19710483]

54. Mettler FA Jr., Huda W, Yoshizumi TT, et al. Effective doses in radiology and diagnostic nuclear medicine: a catalog. Radiology. 2008;248(1):254–263. [PubMed: 18566177]

55. Journy N, Rehel JL, Ducou Le Pointe H, et al. Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a large-scale cohort study in France. Br J Cancer. 2015;112(1):185–193. [PubMed: 25314057]

56. Bernier MO, Rehel JL, Brisse HJ, et al. Radiation exposure from CT in early childhood: a French large-scale multicentre study. Br J Radiol. 2012;85(1009): 53–60. [PubMed: 22190749]

57. Berrington de Gonzalez A, Salotti JA, McHugh K, et al. Relationship between paediatric CT scans and subsequent risk of leukaemia and brain tumours: assessment of the impact of underlying conditions. Br J Cancer. 2016;114(4): 388–394. [PubMed: 26882064]

58. Kim KP, Berrington de González A, Pearce MS, et al. Development of a database of organ doses for paediatric and young adult CT scans in the United Kingdom. Radiat Prot Dosimetry. 2012;150(4):415–426. [PubMed: 22228685]

59. Lubin JH, Adams MJ, Shore R, et al. Thyroid cancer following childhood low dose radiation exposure: a pooled analysis of nine cohorts. J Clin Endocrinol Metab. 2017;102(7):2575–2583. [PubMed: 28323979]

60. Lubin JH, Schafer DW, Ron E, et al. A reanalysis of thyroid neoplasms in the Israeli tinea capitis study accounting for dose uncertainties. Radiat Res. 2004; 161(3):359–368. [PubMed: 14982478]

61. Schafer DW, Lubin JH, Ron E, et al. Thyroid cancer following scalp irradiation: a reanalysis accounting for uncertainty in dosimetry. Biometrics. 2001; 57(3):689–697. [PubMed: 11550916]

62. Werner A, Modan B, Davidoff D. Doses to brain, skull and thyroid, following x-ray therapy for tinea capitis. Phys Med Biol. 1968;13(2):247–258. [PubMed: 5649737]

63. Ahn YS, Park RM, Koh DH. Cancer admission and mortality in workers exposed to ionizing radiation in Korea. J Occup Environ Med. 2008;50(7):791–803. [PubMed: 18617835]

64. Kesminiene A, Evrard AS, Ivanov VK, et al. Risk of hematological malignancies among Chernobyl liquidators. Radiat Res. 2008;170(6):721–735. [PubMed: 19138033]

65. Chumak VV, Romanenko AY, Voilleque PG, et al. The Ukrainian-American study of leukemia and related disorders among Chornobyl cleanup workers from Ukraine: II. Estimation of bone marrow doses. Radiat Res. 2008;170(6): 698–710. [PubMed: 19138037]

66. Muirhead CR, O'Hagan JA, Haylock RG, et al. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. Br J Cancer. 2009;100(1):206–212. [PubMed: 19127272]

67. Muirhead C, O'Hagan J, Haylock R, et al. Third Analysis of the National Registry for Radiation Workers: Occupational Exposure to Ionising Radiation in Relation to Mortality and Cancer Incidence. Chilton, Didcot, Oxfordshire, UK: Health Protection Agency; 2009 Report No. HPA-RPD-062.

68. Jeong M, Jin YW, Yang KH, et al. Radiation exposure and cancer incidence in a cohort of nuclear power industry workers in the Republic of Korea, 1992–2005. Radiat Environ Biophys. 2010;49(1):47–55. [PubMed: 19823862]

69. Boice JD Jr, Cohen SS, Mumma MT, et al. Updated mortality analysis of radiation workers at Rocketdyne (Atomics International), 1948–2008. Radiat Res. 2011;176(2):244–258. [PubMed: 21381866]

70. Boice JD Jr, Leggett RW, Ellis ED, et al. A comprehensive dose reconstruction methodology for former Rocketdyne/Atomics International radiation workers. Health Phys. 2006;90(5):409–430. [PubMed: 16607174]

71. Akiba S, Mizuno S. The third analysis of cancer mortality among Japanese nuclear workers, 1991–2002: estimation of excess relative risk per radiation dose. J Radiol Prot. 2012;32(1):73–83. [PubMed: 22392887]

72. Hosoda Y, Kuba M, Miyake T. First analysis of mortality of nuclear industry workers in Japan, 1986–1992. Hoken Butsuri. 1997;32(2):173–184.

73. Iwasaki T, Murata M, Ohshima S, et al. Second analysis of mortality of nuclear industry workers in Japan, 1986–1997. Radiat Res. 2003;159(2):228–238. [PubMed: 12537528]

74. Zablotska LB, Lane RSD, Thompson PA. A reanalysis of cancer mortality in Canadian nuclear workers (1956–1994) based on revised exposure and cohort data. Br J Cancer. 2014;110(1):214–223. [PubMed: 24231946]

75. Ashmore J, Gentner N, Osborne R. Analysis of the Results for the AECL Cohort in the IARC Study on the Radiogenic Cancer Risk Among Nuclear Industry Workers in Fifteen Countries. Ontario Canada: Atomic Energy of Canada Limited; 2007 Report No. DSP-121100-REPT-001.

76. Ashmore JP, Krewski D, Zielinski JM. Protocol for a cohort mortality study of occupational radiation exposure based on the national dose registry of Canada. Eur J Cancer. 1997;33(suppl 3):S10–S21.

77. Zablotska LB, Ashmore JP, Howe GR. Analysis of mortality among Canadian Nuclear Power Industry Workers after chronic low-dose exposure to ionizing radiation. Radiat Res. 2004;161(6):633–641. [PubMed: 15161357]

78. Zablotska LB, Bazyka D, Lubin JH, et al. Radiation and the risk of chronic lymphocytic and other leukemias among Chornobyl cleanup workers. Environ Health Perspect. 2013;121(1):59–65. [PubMed: 23149165]

79. Kryuchkov V, Chumak V, Maceika E, et al. RADRUE method for reconstruction of external photon doses for Chernobyl liquidators in epidemiological studies. Health Phys. 2009;97(4):275–298. [PubMed: 19741357]

80. Merzenich H, Hammer GP, Tröltzsch K, et al. Mortality risk in a historical cohort of nuclear power plant workers in Germany: results from a second follow-up. Radiat Environ Biophys. 2014;53(2):405–416. [PubMed: 24553629]

81. Schubauer-Berigan MK, Daniels RD, Bertke SJ, et al. Cancer mortality through 2005 among a pooled cohort of U.S. nuclear workers exposed to external ionizing radiation. Radiat Res. 2015;183(6):620–631. [PubMed: 26010709]

82. Richardson DB, Cardis E, Daniels RD, et al. Risk of cancer from occupational exposure to ionising radiation: retrospective cohort study of workers in France, the United Kingdom, and the United States (INWORKS). BMJ. 2015; 351:h5359. [PubMed: 26487649]

83. Leuraud K, Richardson DB, Cardis E, et al. Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study. Lancet Haematol. 2015;2(7): e276–281. [PubMed: 26436129]

84. Thierry-Chef I, Marshall M, Fix JJ, et al. The 15-country collaborative study of cancer risk among radiation workers in the nuclear industry: study of errors in dosimetry. Radiat Res. 2007;167(4):380–395. [PubMed: 17388692]

85. Caldwell GG, Zack MM, Mumma MT, et al. Mortality among military participants at the 1957 PLUMBBOB nuclear weapons test series and from leukemia among participants at the SMOKY test. J Radiol Prot. 2016;36(3):474–489. [PubMed: 27355245]

86. Till JE, Beck HL, Aanenson JW, et al. Military participants at U.S. atmospheric nuclear weapons testing-methodology for estimating dose and uncertainty. Radiat Res. 2014;181(5):471–484. [PubMed: 24758578]

87. National Research Council. A Review of the Dose Reconstruction Program of the Defense Threat Reduction Agency. Washington, DC: National Academies Press; 2003.

88. National Research Council. Film Badge Dosimetry in Atmospheric Nuclear Tests. Washington, DC: National Academy Press; 1989.

89. Preston DL, Kitahara CM, Freedman DM, et al. Breast cancer risk and protracted low-to-moderate dose occupational radiation exposure in the US radiologic technologists cohort, 1983–2008. Br J Cancer. 2016;115(9):1105–1112. [PubMed: 27623235]

90. Lee T, Sigurdson AJ, Preston DL, et al. Occupational ionising radiation and risk of basal cell carcinoma in US radiologic technologists (1983–2005). Occup Environ Med. 2015;72(12):862–869. [PubMed: 26350677]

91. Kitahara CM, Linet MS, Balter S, et al. Occupational radiation exposure and deaths from malignant intracranial neoplasms of the brain and CNS in U.S. radiologic technologists, 1983–2012. AJR Am J Roentgenol. 2017;208(6): 1278–1284. [PubMed: 28350475]

92. Simon SL, Preston DL, Linet MS, et al. Radiation organ doses received in a nationwide cohort of U.S. radiologic technologists: methods and findings. Radiat Res. 2014;182(5):507–528. [PubMed: 25361400]

93. Simon SL. Organ-specific external dose coefficients and protective apron transmission factors for historical dose reconstruction for medical personnel. Health Phys. 2011;101(1):13–27. [PubMed: 21617389]

94. Simon SL, Weinstock RM, Doody MM, et al. Estimating historical radiation doses to a cohort of U.S. radiologic technologists. Radiat Res. 2006;166(1): 174–192. [PubMed: 16808606]

95. Leuraud K, Fournier L, Samson E, et al. Mortality in the French cohort of nuclear workers. Radioprotection. 2017;52(3):199–210.

96. Laurent O, Metz-Flamant C, Rogel A, et al. Relationship between occupational exposure to ionizing radiation and mortality at the French electricity company, period 1961–2003. Int Arch Occup Environ Health. 2010;83(8): 935–944. [PubMed: 20148259]

97. Metz-Flamant C, Samson E, Caer-Lorho S, et al. Solid cancer mortality associated with chronic external radiation exposure at the French atomic energy commission and nuclear fuel company. Radiat Res. 2011;176(1):115–127. [PubMed: 21476856]

98. Goldhaber MK, Tokuhata GK, Digon E, et al. The Three Mile Island Population Registry. Public Health Rep. 1983;98(6):603–609. [PubMed: 6419276]

99. Beck HL, Till JE, Grogan HA, et al. Red bone marrow and male breast doses for a cohort of atomic veterans. Radiat Res. 2017;187(2):221–228. [PubMed: 28135126]

100. Murata M, Miyake T, Inoue Y, et al. Life-style and other characteristics of radiation workers at nuclear facilities in Japan: base-line data of a questionnaire survey. J Epidemiol. 2002;12(4):310–319. [PubMed: 12395871]

101. Schubauer-Berigan MK, Daniels RD, Fleming DA, et al. Chronic lymphocytic leukaemia and radiation: findings among workers at five US nuclear facilities and a review of the recent literature. Br J Haematol. 2007;139(5):799–808. [PubMed: 17922878]

102. Schubauer-Berigan MK, Daniels RD, Fleming DA, et al. Risk of chronic myeloid and acute leukemia mortality after exposure to ionizing radiation among workers at four U.S. nuclear weapons facilities and a nuclear naval shipyard. Radiat Res. 2007;167(2):222–232. [PubMed: 17390730]

103. Daniels RD, Bertke S, Waters KM, et al. Risk of leukaemia mortality from exposure to ionising radiation in US nuclear workers: a pooled case-control study. Occup Environ Med. 2013;70(1):41–48. [PubMed: 23000827]

104. Fournier L, Laurent O, Samson E, et al. External radiation dose and cancer mortality among French nuclear workers: considering potential confounding by internal radiation exposure. Int Arch Occup Environ Health. 2016;89(8): 1183–1191. [PubMed: 27383840]

105. Fournier L, Clero E, Samson E, et al. Impact of considering non-occupational radiation exposure on the association between occupational dose and solid cancer among French nuclear workers. Occup Environ Med. 2018;75(3): 199–204. [PubMed: 29055886]

106. Flamant C, Samson E. Etude CEA-COGEMA: Validation de la Dosimétrie du CEA Civil de 1957 à 1967. Impact Sur la Relation Dose-effet. Note technique IRSN/DRPH/SRBE/LEPID 04–730. Institut de Radioprotection et de Suˆreté Nucleáire (IRSN), Fontenay-aux-roses, France: ISRN; 2004.

107. Telle-Lamberton M, Samson E, Caer S, et al. External radiation exposure and mortality in a cohort of French nuclear workers. Occup Environ Med. 2007; 64(10):694–700. [PubMed: 17522135]

108. United Nations Scientific Committee on the Effects of Atomic Radiation(UNSCEAR). Epidemiological studies of cancer risk due to low-dose-rate radiation from environmental sources, Annex B In: UNSCEAR 2017 Report to the General Assembly with Scientific Annexes. Sources, Effects and Risks of Ionizing Radiation. New York, NY: UNSCEAR; 2018.

109. Tao Z, Zha Y, Akiba S, et al. Cancer mortality in the high background radiation areas of Yangjiang, China during the period between 1979 and 1995. J Radiat Res. 2000;41(suppl):31–41. [PubMed: 11142210]

110. Schubauer-Berigan MK, Berrington de González A, Cardis E, et al. Evaluationof confounding and selection bias in epidemiologic studies of populations exposed to low-dose, high-energy photon radiation. JNCI Monographs. 2020;2020(56):133–153.

111. Degteva MO, Shagina NB, Tolstykh EI, et al. An approach to reduction ofuncertainties in internal doses reconstructed for the Techa River population. Radiat Prot Dosimetry. 2007;127(1–4):480–485. [PubMed: 17848387]

112. Degteva MO, Anspaugh LR, Akleyev AV, et al. Electron paramagnetic resonance and fluorescence in situ hybridization-based investigations of individual doses for persons living at Metlino in the upper reaches of the Techa River. Health Phys. 2005;88(2):139–153. [PubMed: 15650589]

113. Degteva MO, Shagina NB, Shishkina EA, et al. Analysis of EPR and FISH studies of radiation doses in persons who lived in the upper reaches of the Techa River. Radiat Environ Biophys. 2015;54(4):433–444. [PubMed: 26205380]

114. Taranenko V, Meckbach R, Degteva MO, et al. Verification of external exposure assessment for the upper Techa riverside by luminescence measurements and Monte Carlo photon transport modeling. Radiat Environ Biophys. 2003;42(1):17–26. [PubMed: 12687379]

115. Vozilova AV, Shagina NB, Degteva MO, et al. Fish analysis of translocations induced by chronic exposure to Sr radioisotopes: second set of analysis of the Techa River Cohort. Radiat Prot Dosimetry. 2014;159(1–4):34–37. [PubMed: 24743760]

116. Vozilova AV, Shagina NB, Degteva MO, et al. Preliminary FISH-based assessment of external dose for residents exposed on the Techa River. Radiat Res. 2012;177(1):84–91. [PubMed: 22026585]

117. Napier BA, Degteva MO, Tolstykh EI, et al. Descriptions of Dose Distributions with Uncertainties for Members of the Techa River and East Urals Radioactive Trace Cohorts. US-Russian Joint Coordinating Committee on Radiation Effects Research, Project 1.1, Pacific Northwest National Laboratory (PNNL) and Urals Research Center for Radiation Medicine. Richland, WA: PNNL; 2018.

118. Hwang SL, Hwang JS, Yang YT, et al. Estimates of relative risks for cancers in a population after prolonged low-dose-rate radiation exposure: a follow-up assessment from 1983 to 2005. Radiat Res. 2008;170(2):143–148. [PubMed: 18666807]

119. Chang WP, Hwang BF, Wang D, et al. Cytogenetic effect of chronic low-dose, low-dose-rate gamma-radiation in residents of irradiated buildings. Lancet. 1997;350(9074):330–333. [PubMed: 9251638]

120. Liu RS, Chen WL, Chen FD. Health examination and chromosome aberration analysis of residents living in 60Co-contaminated rebar buildings. Int J Radiat Biol. 2002;78(7):635–639. [PubMed: 12079543]

121. Tucker JD, Luckinbill LS. Estimating the lowest detectable dose of ionizing radiation by FISH whole-chromosome painting. Radiat Res. 2011;175(5): 631–637. [PubMed: 21443424]

122. Furukawa K, Preston D, Funamoto S, et al. Long-term trend of thyroid cancer risk among Japanese atomic-bomb survivors: 60 years after exposure. Int J Cancer. 2013;132(5):1222–1226. [PubMed: 22847218]

123. Preston DL, Ron E, Tokuoka S, et al. Solid cancer incidence in atomic bomb survivors: 1958–1998. Radiat Res. 2007;168(1):1–64. [PubMed: 17722996]

124. Sadetzki S, Chetrit A, Lubina A, et al. Risk of thyroid cancer after childhood exposure to ionizing radiation for tinea capitis. J Clin Endocrinol Metab. 2006; 91(12):4798–4804. [PubMed: 17018661]

125. Daniels RD, Bertke SJ, Richardson DB, et al. Examining temporal effects on cancer risk in the international nuclear workers' study. Int J Cancer. 2017; 140(6):1260–1269. [PubMed: 27914102]

126. Richardson DB, Cardis E, Daniels RD, et al. Site-specific solid cancer mortality after exposure to ionizing radiation: a cohort study of workers (INWORKS). Epidemiology. 2018;29(1):31–40. [PubMed: 28991003]

127. Xue X, Kim MY, Shore RE. Estimation of health risks associated with occupational radiation exposure: addressing measurement error and minimum detectable exposure level. Health Phys. 2006;91(6):582–591. [PubMed: 17099402]

128. Frome EL, Cragle DL, Watkins JP, et al. A mortality study of employees of the nuclear industry in Oak Ridge, Tennessee. Radiat Res. 1997;148(1):64–80. [PubMed: 9216620]

129. Little MP, Kendall GM, Muirhead CR, et al. Further analysis, incorporating assessment of the robustness of risks of cancer mortality in the National Registry for Radiation Workers. J Radiol Prot. 1993;13(2):95–108.

130. Anderson JL, Daniels RD. Bone marrow dose estimates from work-related medical x-ray examinations given between 1943 and 1966 for personnel from five U.S. nuclear facilities. Health Phys. 2006;90(6):544–553. [PubMed: 16691102]

131. Daniels RD, Kubale TL, Spitz HB. Radiation exposure from work-related medical x-rays at the Portsmouth Naval Shipyard. Am J Ind Med. 2005;47(3): 206–216. [PubMed: 15712259]

132. Cardarelli J, Spitz H, Rice C, et al. Significance of radiation exposure from work-related chest x-rays for epidemiological studies of radiation workers. Am J Ind Med. 2002;42(6):490–501. [PubMed: 12439872]

133. Laborde-Castérot H, Laurier D, Caër-Lorho S, et al. Chest x-ray screening examinations among French uranium miners: exposure estimation and impact on radon-associated lung cancer risk. Occup Environ Med. 2014;71(9): 611–618. [PubMed: 25017574]

134. Kubale TL, Daniels RD, Yiin JH, et al. A nested case-control study of leukemia mortality and ionizing radiation at the Portsmouth Naval Shipyard. Radiat Res. 2005;164(6):810–819. [PubMed: 16296888]

135. Yiin JH, Anderson JL, Daniels RD, et al. A nested case-control study of multiple myeloma risk and uranium exposure among workers at the Oak Ridge Gaseous Diffusion Plant. Radiat Res. 2009;171(6):637–645. [PubMed: 19580470]

136. Yiin JH, Silver SR, Daniels RD, et al. A nested case-control study of lung cancer risk and ionizing radiation exposure at the Portsmouth Naval Shipyard. Radiat Res. 2007;168(3):341–348. [PubMed: 17705634]

137. Yiin JH, Anderson JL, Bertke SJ, et al. Dose-response relationships between internally-deposited uranium and select health outcomes in gaseous diffusion plant workers, 1948–2011. Am J Ind Med. 2018;61(7):605–614. [PubMed: 29744908]

138. Gilbert ES, Fix JJ. Laboratory Measurement Error in External Dose Estimates and Its Effects on Dose-Response Analyses of Hanford Worker Mortality Data. Richland, WA: Pacific Northwest National Laboratory (PNNL); 1996 Report No. PNNL11289.

139. Little MP, Kwon D, Doi K, et al. Association of chromosome translocation rate with low dose occupational radiation exposures in U.S. radiologic technologists. Radiat Res. 2014;182(1):1–17. [PubMed: 24932535]

140. Chumak VV. Physical dosimetry of Chernobyl cleanup workers. Health Phys. 2007;93(5):452–461. [PubMed: 18049221]

141. Bouville A, Chumak VV, Inskip PD, et al. The Chornobyl accident: estimation of radiation doses received by the Baltic and Ukrainian cleanup workers. Radiat Res. 2006;166(1):158–167. [PubMed: 16808604]

142. Cardis E, Gilbert ES, Carpenter L, et al. Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. Radiat Res. 1995;142(2):117–132. [PubMed: 7724726]

143. Romanenko A, Bebeshko V, Hatch M, et al. The Ukrainian-American stud yof leukemia and related disorders among Chornobyl cleanup workers from Ukraine: I. Study methods. Radiat Res. 2008;170(6):691–697. [PubMed: 19138036]

144. Kesminiene A, Evrard AS, Ivanov VK, et al. Risk of thyroid cancer among Chernobyl liquidators. Radiat Res. 2012;178(5):425–436. [PubMed: 22998226]

Table 1.

Major types and sources of dose estimation error in low-dose radioepidemiologic studies[*]

Source	Description	Potential effect on dose-response	Common correction
All			
Classical measurement error	Random (sampling) error in dose measurements, eg, the random error from an imprecise measurement device such as a film dosimeter	Loss of power. The effect depends on the error magnitude. A nondifferential classical error generally weakens the dose-response with linear risk coefficients biased towards zero (10, 11).	Dose-response models can be adjusted for random error using regression calibration or maximum likelihood methods (11).
Berkson measurement error	Error that occurs when the mean for a group is substituted for the individual dose within the group, eg, the use of a single factor to convert "recorded" external doses to organ doses results in Berkson error.	Loss of power. The effect depends on the error magnitude. Generally, Berkson error results in very little bias (12).	There is little need for adjustment.
Shared error	When there is error in a group mean assigned to all of the individuals in a group, or in a parameter used to calculate a quantity common to a group, this error is "shared" among those individuals.	Biased risk estimation (due to misspecification of group mean values and understatement of uncertainty due to correlated [nonindependent] dosimetry errors)	Dose error adjustments based on complex Monte Carlo simulation techniques are being applied in some analyses. These methods reduce bias and increase confidence interval width to reflect the correlated dose errors.
Differential and nondifferential error	Dose estimation error that is independent of case status (and other predictors) is said to be nondifferential. Sources of differential error include data collection bias from different recalls of cases compared to controls (ie, recall bias) or from selective data gathering by the exposure assessor (ie, observer or interviewer bias).	Nondifferential error commonly results in bias toward a null association; however, there are examples of nondifferential error in polytomous and continuous exposure measures that induce bias away from the null (13–15). Differential error can result in bias in either direction and can lead to spurious associations.	Collect exposure data prior to disease ascertainment or without prior knowledge of the hypothesized association. Keep exposure assessors blinded to case status.
Missing dose	Doses from occupational, environmental, and medical sources that were accrued by study subjects but were not accounted for in dose-response analyses, for example, historic practices of not measuring doses that were thought at the time to be trivial.	The bias can be in either direction, depending on the distribution of unmonitored dose among study participants.	Use evidence-based dose assignments to fill data gaps in exposure histories.
Environmental			
Model validation	Indirectly obtained dose estimates should undergo some model validation. Model validation is the process of establishing the quality of dose estimates of being logically or factually sound (ie, the extent to which the estimate describes the true dose that is being measured).	The weight of evidence from a study relying on models is less if those models have not been validated.	Conduct intercomparisons of estimated from measurements and other dosimetry systems.
Group heterogeneity	Variance in true dose within the group of individuals assigned group-level estimates	Loss of power. The magnitude of variance depends on the resolution of the measurement and the homogeneity of the group (see Berkson error).	Identify similarly exposed groups.
Occupancy	Incomplete information on location and/or time when dose is estimated based on the product of the duration of time exposed and mean dose at a known location	Loss of power. Bias in either direction depending on the treatment of unmeasured exposure.	
Medical			
Missing data on patients	Lack of information on the physical characteristics of the patients (height and weight) with age often used as a surrogate	Unshared uncertainty	Impute height and weight based on growth curves could be performed. However, imputation strategy should avoid introducing biased values and thus systematic errors to the whole group.

Source	Description	Potential effect on dose-response	Common correction
Missing data on protocols	Lack of detailed information on specific protocol implemented for each individual examination. Typically, protocols are followed in ways that vary among individuals.	Shared uncertainties on imputed values with some uncertain individual variability	Impute values based on typical protocols implemented in the hospital are usually performed. However, imputation strategy should avoid introducing biased values and, thus, systematic errors to the whole group.
Uncertainty in the model and/or in phantom measurements	Uncertainties associated with on-phantom measurements, prediction equation parameters, and model specification	Shared uncertainty	Validate models with additional measurements.
Occupational			
Unadjusted dose	Recorded doses that poorly estimate the absorbed dose to target tissues, which is the preferred quantity for use in dose-response analyses (16). This is an example of shared error.	For most exposure situations, using unadjusted doses in risk models will underestimate the dose-response association.	Adjust recorded dose to account for exposure geometry and incident radiation energies that differ from the calibration and dose quantitation protocols used (17–20).
Below detection limit (BDL) doses	Inaccurate estimates of dose resulting from treatment of exposures at levels below the minimum detection level of the instrument. The potential for this error is greatest in doses accrued prior to the 1960s, when dosimeters were least sensitive and weekly or biweekly monitoring was routine.	The bias can be in either direction, depending primarily on the exposure distribution, the BDL dose value assigned, and the variance in the measured exposure due to random measurement error (21).	Adjust recorded dose by substitution, multiple imputation, or other means to account for BDL doses (22–24).
Notional dose	Dose assigned to a worker's dose record to account for exposures that were not quantified. These assignments were often based on a maximum allowable dose to prevent exceeding limits from subsequent exposure. The effects are likely minimized if assignments were realistic exposure scenarios or used data from measurements made in similar time and place.	The bias can be in either direction depending primarily on the distribution of notional dose among study participants.	Replace notional dose assignments with evidence-based dose estimates (25, 26).

*
Sources that are perceived to contribute substantially to dose estimation errors in study categories. Although listed for a single category, a source may contribute to errors in multiple categories.

Table 2.

Dosimetry and other characteristics of selected radiation epidemiology studies post–BEIR VII

ID	Study group or name	Exposure period	Exposed subjects	Average (range) dose: target	Dose metric	Study reference	Dosimetry reference(s)
	Environmental						
1	Chernobyl residents	1986–2000	1 256	6 (0–265) mGy, RBM *	Absorbed dose	(28)	NA
2	TMI residents	1979	21 494	0.10 (0–0.80) mSv †	$H_p(10)$	(29)	(30, 31)
3	Chinese background	1905–1998	31 604	66 (0–125+) mGy, colon ‡	Absorbed dose	(32)	(33–35)
4	GB background	1991–1996	64 240	4 (0–31) mSv, RBM *	Equivalent dose	(36)	(37–40)
5	Swiss background	1974–2008	2 093 660	9 (0–49) mSv	Equivalent dose	(41)	(42, 43)
6	Techa River residents	1951–2007	17 435	60 (0–960) mGy, stomach §	Absorbed dose	(44)	(45–47)
7	Finnish background	1990–2011	4 372	2 (0–12) mSv, RBM *, ‖	Equivalent dose	(48)	
8	Taiwanese residents	1982–1995	6 242	48 (0–2363) mSv	Equivalent dose	(49)	(50, 51)
	Medical						
9	Cardiac imaging patients	1996–2006	82 861	5.3 mSv per patient-year	Equivalent dose	(52)	(53, 54)
10	French pediatric CT	2000–2010	67 274	23 (0–100+) mGy: brain; 9 (0–100+), RBM	Absorbed dose	(55)	(56)
11	UK pediatric CT	1980–2002	178 604	43 (0–350+), brain; 12 (0–50+) mGy, RBM	Absorbed dose	(57)	(58)
12	PIRATES (low-dose)	1926–2000	107 594	30 (0–200) mGy, thyroid	Absorbed dose	(59)	(60–62)
	Occupational						
13	Korean NW	1984–2004	79 679	6 (0–50+) mSv	Effective dose	(63)	NA
14	Russian CL	1986–1987	357	51 (0–500+) mGy, RBM ¶	Absorbed dose	(64)	(65)
15	UKNRRW	1946–2001	174 541	25 (0–600+) mSv	Equivalent dose	(66)	(25, 67)
16	Korean NPW	1978–2005	16 236	20 (0–480) mSv	Effective dose	(68)	NA
17	Rocketdyne NW	1948–1999	5 801	14 (0–1000) mSv #	Equivalent dose	(69)	(70)
18	Japanese NW	1957–2002	200 583	12 (0–<450) mSv **	Effective dose	(71)	(72, 73)
19	Canadian NW	1956–1994	45 316	22 (0–679) mSv	Equivalent dose	(74)	(75–77)
20	Ukrainian CL	1986–1987	1 000	82 (0–2600) mGy, RBM *	Absorbed dose	(78)	(65, 79)
21	German NPW	1966–2008	8 972	30 (0–100+) mSv	Effective dose	(80)	NA
22	US NW	1944–2005	119 195	20 (0–700) mSv	$H_p(10)$	(81)	NA
23	INWORKS	1944–2005	308 297	21 (0–1332) mGy, colon; 16 (0–1218) mGy, RBM	Absorbed dose	(82, 83)	(17, 84)

ID	Study group or name	Exposure period	Exposed subjects	Average (range) dose: target[††]	Dose metric	Study reference	Dosimetry reference(s)
24	US atomic veterans	1945–1963	114 270	9 (0–580) mGy, RBM[††]	Absorbed dose	(85)	(86–88)
25	USRT	1916–1997	66 915, breast; 110 297, brain; 65 719, skin	37 (0–100+) mGy, breast; 12 (0–290) mGy, brain; 56 (0–1735) mGy, skin	Absorbed dose	(89–91)	(92–94)
26	French NW	1950–2004	59 004	26 (0–669) mSv	$H_p(10)$	(95)	(96, 97)

[*] Values shown are for control population. BEIR = biological effects of ionizing radiation; CL = Chernobyl liquidators; CT = computed tomography; GB = Great Britain; $H_p(10)$ = personal dose equivalent; INWORKS = International Nuclear Workers Study; NA = not applicable; NPW = nuclear power workers; NuTRIS = Nuclear Test Review Program Information System; NW = nuclear workers; PIRATES = Pooled International Radiation and Thyroid Cancer Epidemiology Studies; RBM = red bone marrow; TMI = Three Mile Island; UKNRRW = UK National Registry for Radiation Workers; USRT = US Radiologic Technologists.

[†] Values shown are described as "likely" skin dose values. Range is from Gur et al. (98).

[‡] Person-year weighted average is shown.

[§] From Davis et al. (44).

[‖] Median dose is shown.

[¶] Estimated from dose distribution.

[#] External dose only.

[**] Upper bound from Iwasaki et al. (73).

[††] Adjusted NuTRIS dose from Beck et al. (99).

Table 3.

Key strengths and weaknesses of selected radiation epidemiology studies post–BEIR VII[*]

ID	Study group or name	Main strengths	Main weaknesses	Study reference(s)
	Environmental			
1	Chernobyl residents	Dose estimates based on detailed analysis; significant cross-validation	Potential for recall bias; contribution from complex internal dosimetry	(28)
2	TMI residents	Dose estimates based on detailed analysis; some validation of dose estimates from environmental monitoring	Sparse measurement data; plume model was complex and thus error-prone; intentionally conservative assumptions used	(29)
3	Chinese background	Detailed modeling based on extensive indoor and outdoor measurements; significant dose validation	Small potential for recall bias	(32)
4	GB background	Dose estimates based on indoor measurements; no differences between cases and controls	Dose estimates for areas larger than ideal; no residential histories	(36)
5	Swiss background	No case and controls differences; dose estimates for 2×2 km grid	Dose estimates only for outdoor radiation	(41)
6	Techa River residents	Dose estimates based on detailed analysis; significant cross-validation; medical exposures included	Contribution from complex internal dosimetry	(44)
7	Finnish background	No case and controls differences; full residential histories available	Crude conversion from outdoor to indoor dose; dose estimates for 8×8 km grid, larger than ideal	(48)
8	Taiwanese residents	Dosimetric scheme based on numerous measurements	Dosimetry dependent on detailed recollection of occupancy; small potential of recall bias	(49)
	Medical			
9	Cardiac imaging patients	Used simple and reproducible dosimetry methods	Used effective dose; used average protocol doses; no information on assessment of noncardiac exposures; dose error not assessed	(52)
10	French pediatric CT	Used organ absorbed dose	Specific protocol parameters not available; analyses did not consider dose from other diagnostic examinations	(55)
11	UK pediatric CT	Used organ absorbed dose	Specific protocol parameters not available; analyses did not consider dose from other diagnostic examinations	(57)
12	PIRATES (low dose)	Used organ absorbed dose; analysis of dose estimation errors; adjusted for random error using regression calibration	Specific protocol parameters were not available	(59)
	Occupational			
13	Korean NW	Measurements from personal monitoring including incorporated radionuclides and neutron dose	Used unadjusted recorded dose; dose from WRX not assessed, although fluoroscopic and photofluorographic procedures unlikely	(63)
14	Russian CL	Dose estimates based on detailed analysis; individual estimates of absorbed dose to tissues and organs of interest, adjusted for dose error; model validation; advanced treatment of dose estimation errors	Sparse measurement data; complex exposures; potential for recall bias	(64)
15	UKNRRW	Measurements from personal monitoring; adjustment for missed and notional doses; evaluation of dose estimation errors by sensitivity analysis	Used unadjusted recorded dose; dose from WRX, neutrons, and internal exposures not assessed	(66)
16	Korean NPW	Measurements from personal monitoring, including incorporated radionuclides and neutron dose	Used unadjusted recorded dose; dose from WRX not assessed, although fluoroscopic and photofluorographic procedures unlikely	(68)

ID	Study group or name Environmental	Main strengths	Main weaknesses	Study reference(s)
17	Rocketdyne NW	Measurements from personal monitoring including neutrons; major efforts to reconstruct significant dose contributions from incorporated radionuclides	Used unadjusted recorded dose; assessment of internal dose restricted to a few participants; dose from WRX not assessed	(69)
18	Japanese NW	Measurements from personal monitoring including incorporated radionuclides and neutron dose	Used unadjusted recorded dose; dose from WRX not assessed, although some evidence of an inverse relationship between cumulative dose and number of x-ray exams among radiation workers (100)	(71)
19	Canadian NW	Measurements from personal monitoring, including assessment of tritium dose	Used unadjusted recorded dose; potentially incomplete dose histories; dose from WRX, neutrons, and incorporated radionuclides (other than tritium) not assessed; however, workers with recorded neutron dose or "high" internal exposures excluded	(74)
20	Ukrainian CL	Dose estimates based on detailed analysis; individual estimates of absorbed dose to tissues and organs of interest, adjusted for dose error; model validation; advanced treatment of dose estimation errors	Sparse measurement data; complex exposures; potential for recall bias	(78)
21	German NPW	Measurements from personal monitoring including incorporated radionuclides and neutron dose	Used unadjusted recorded dose; dose from WRX not assessed	(80)
22	US NW	Measurements from personal monitoring, including neutron and tritium doses; WRX, neutron exposures, and plutonium uptakes examined in previous case-control studies of leukemia mortality (101–103)	Used unadjusted recorded dose; dose from WRX, internal exposures (excluding tritium) not assessed	(81)
23	INWORKS	Measurements from person monitoring; dose estimates based on detailed analysis to derive absorbed dose to tissues and organs of interest, adjusted for systematic dose error	Dose from WRX, neutrons, and incorporated radionuclides not assessed	(82, 83)
24	US atomic veterans	Model validation by intercomparison with another dose reconstruction	Sparse measurement data; random error not accounted for in dose-response analysis	(85)
25	USRT	Dose estimates based on detailed analysis; model validation; advanced treatment of dose estimation errors	Sparse data from personal monitoring, especially for early exposures	(89–91)
26	French NW	Measurement from personal monitoring; dose estimates based on detailed analysis; adjusted for systematic dose error; measurements from personal monitoring; companion papers examined confounding effects from internal exposures (104) and exposures to environmental and medical sources (105); missed dose examined in previous analyses (106, 107)	Dose from neutrons and internal exposures not assessed	(95)

*
BEIR = biological effects of ionizing radiation; CL = Chernobyl liquidators; CT = computed tomography; GB = Great Britain; INWORKS = International Nuclear Workers Study; NPW = nuclear power workers; NW = nuclear workers; PIRATES = Pooled International Radiation and Thyroid Cancer Epidemiology Studies; TMI = Three Mile Island; UKNRRW = United Kingdom National Registry for Radiation Workers; USRT = US Radiologic Technologists; WRX = work-related x-ray examinations.

Table 4.

Information on neutron and incorporated radionuclide exposures in occupational radiation epidemiology studies post–BEIR VII[*]

ID	Study name(s)	Exposure source	Information on exposures		Treatment in dose-response analysis	
			Neutron	Internal	Neutron	Internal
13	Korean NW	Reactor operations, research, medical services, general industry NDT, military	NR, similar to study ID 16	NR, similar to study ID 16	NR, similar to study ID 16	NR, similar to study ID 16
14, 20	Belarus, Russia and Baltic CL; Ukrainian CL	Cleanup of fission product surface contamination on building materials and ground	NA	Internal dose to RBM resulting from incorporated radionuclides (eg, ^{90}Sr, ^{137}Cs, and ^{239}Pu) was determined to be negligible.	NA	None
15	UKNRRW NW	Reactor operations, accelerator use, research, plutonium production, military	Neutron dose was integrated into the dose of record.	NR	Included in dose metric	Dichotomous exposure variable to indicate workers ever or never monitored for internal emitters (n = 22 000). Multiple sensitivity analyses conducted. For all cancer, excluding workers monitored for internal exposure, resulted in an increase of the ERR/Sv (all persons ERR/Sv = 0.28, 90% CI = 0.02 to 0.56; restricted ERR/Sv =0.76, 90% CI = 0.22 to 1.38); however, adjusting for monitoring status did not appreciably influence central estimates (ERR/Sv = 0.29, 90% CI = 0.01 to 0.60).
16	Korean male NP NW	Reactor operations	7.8% of cohort with mean dose equivalent from neutron exposures >10% of total dose	26% of cohort had a record of internal dose. Of these, the mean committed dose was 0.82 mSv.	Included in dose metric	Included in dose metric
17	Rocketdyne NW	Reactor operations, uranium fuel fabrication, plutonium fuel fabrication	About 11.4% of workers were monitored. Of these, 50% had recorded doses >0, <2% with total neutron dose >10 mSv.	42% of radiation workers were monitored. Most had a committed dose <10 mSv. Organ-committed equivalent doses were reconstructed from available data for <300 workers.	Included in dose metric	Included in dose metric except for analysis of "all cancer excluding leukemia." The effects of including internal dose in dose-response analyses were not assessed.
18	Japanese male NW	Reactor operations, fuel processing, accelerators, research	NR	The previous analysis (73) reported that the committed dose was "almost negligible."	Included in dose metric	Included in dose metric
19	Canadian NW	Reactor operations	Workers with recorded neutron dose were excluded (n = 15).	NA. Workers with "high" internal exposures (except for tritium) were excluded (n = 10). Tritium dose was assessed as whole-body equivalent dose. The mean person-time weighted dose from tritium was approximately 3 mSv (14% of	NA	Tritium included in primary dose metric. The joint effects of external and tritium doses were examined using separate terms. These models did not exhibit improved fit.

			Information on exposures		Treatment in dose-response analysis	
ID	Study name(s)	Exposure source	Neutron	Internal	Neutron	Internal
21	German NP NW	Reactor operations	Dose to neutrons reported as "negligible."	NR	Included in dose metric	Effective dose is reported; therefore, assumed to be included in dose metric.
22	US NW	Reactor operations, accelerator use, plutonium production, tritium production	Included in dose metric	Tritium dose was quantified and included in the dose metric (<5% of total dose). Workers with committed dose or indication of a positive uptake (1.9% of cohort) were flagged as potentially internally exposed.	Neutron dose inclusion or exclusion made little difference in risk estimates in sensitivity analyses. For all cancers with and without neutron and tritium dose: with: ERR/Sv = 0.14, 95% CI = −0.17 to 0.48; without: ERR/Sv = 0.18, 95% CI = −0.14 to 0.53.	Tritium dose inclusion or exclusion made little difference in risk estimates in sensitivity analyses. Based on small numbers potentially exposed, the authors concluded that there was little evidence of a potential bias from unmeasured internal contamination.
23	INWORKS NW	Reactor operations, accelerator use, plutonium production, tritium production	Records were not available for all facilities or over all monitoring periods. When monitoring for neutrons, some facilities included contribution in the worker's dose of record without adequate information to distinguish from other sources of exposure.	Records were not available for all facilities or over all monitoring periods. Available measures varied and included positive bioassay results, confirmed uptake (eg, fraction of body burden or annual limit on intake), or an assigned committed dose. Tritium doses were combined with external doses in some facilities.	Included as a time-varying indicator for each worker, classifying them according to whether they had a positive recorded neutron dose (9% of cohort), and if so, whether their neutron dose ever exceeded 10% of their total external penetrating radiation dose (4% of cohort). Sensitivity analyses were conducted excluding workers with reported neutron dose. For all cancers other than leukemia: full: ERR/Gy = 0.48, 90% CI = 0.20 to 0.79; reduced: ERR/Gy = 0.55, 90% CI = 0.17 to 0.95.	Dichotomous exposure variable: those with known (or suspected) deposition (17% of cohort) vs those with no contamination Sensitivity analyses were conducted excluding workers flagged for internal contamination. For all cancers other than leukemia: full: ERR/Gy = 0.48, 90% CI = 0.20 to 0.79; reduced: ERR/Gy = 0.72, 90% CI = 0.29 to 1.19. Analysis of solid cancer excluding cancers of the lung, liver, and bone, which are three sites that receive substantial doses from incorporated plutonium. The ERR/Gy (0.51, 90% CI = 0.15 to 0.91) was similar to that for all solid cancers.
24	US atomic veterans	Prompt and delayed radiation from nuclear detonation. Most dose from descending, suspended, or deposited fallout.	NR, dose from neutron exposure was small compared with gamma dose and mostly limited to small numbers of observers in trenches close to ground zero (87).	NR, previous analyses suggest that RBM dose from internal emitters would be "no more than a few percent of the dose" from external sources (86).	Included in dose metric	NR
25	USRT female RT	Exposures to x-rays from medical diagnostic and therapeutic procedures	NA	NA	NA	NA
26	French NW	Reactor operations, accelerator use, plutonium production	Sparse monitoring data were available beginning in 1967.	Sparse data on internal contamination were available in some facilities.	Time-varying indicator for workers, classifying them according to whether they had a potentially substantial neutron dose. 11% of person-years were	Adjustments not made based on findings in a companion analysis, which indicated no evidence of a strong bias from exclusion of internal dose information (104). For solid cancer mortality: adjusted ERR/Sv = 0.21,

		Information on exposures		Treatment in dose-response analysis	
ID	Study name(s)	Exposure source	Neutron	Internal	Neutron	Internal
					ever exposed to neutrons. Adjusting for neutron exposure had negligible effects on solid cancer risk estimates (adjusted ERR/Sv = 0.37, 90% CI = −0.44 to 1.30; unadjusted ERR/Sv = 0.36, 90% CI = −0.42 to 1.25). Leukemia risk was attenuated slightly with adjustment for neutrons (adjusted ERR/Sv = 2.22, 90% CI = <0 to 14.13; unadjusted ERR/Sv = 3.52, 90% CI = <0 to 16.00).	90% CI = −0.68 to 1.23; unadjusted ERR/Sv = 0.32, 90% CI = −0.58 to 1.35)