

## **Estimating Risk of Low Radiation Doses – A Critical Review of the BEIR VII Report and its Use of the Linear No-Threshold (LNT) Hypothesis**

Authors: Calabrese, Edward J., and O'Connor, Michael K.

Source: Radiation Research, 182(5) : 463-474

Published By: Radiation Research Society

URL: <https://doi.org/10.1667/RR13829.1>

---

BioOne Complete ([complete.BioOne.org](https://complete.BioOne.org)) is a full-text database of 200 subscribed and open-access titles in the biological, ecological, and environmental sciences published by nonprofit societies, associations, museums, institutions, and presses.

Your use of this PDF, the BioOne Complete website, and all posted and associated content indicates your acceptance of BioOne's Terms of Use, available at [www.bioone.org/terms-of-use](https://www.bioone.org/terms-of-use).

Usage of BioOne Complete content is strictly limited to personal, educational, and non - commercial use. Commercial inquiries or rights and permissions requests should be directed to the individual publisher as copyright holder.

---

BioOne sees sustainable scholarly publishing as an inherently collaborative enterprise connecting authors, nonprofit publishers, academic institutions, research libraries, and research funders in the common goal of maximizing access to critical research.

## COMMENTARY

# Estimating Risk of Low Radiation Doses – A Critical Review of the BEIR VII Report and its Use of the Linear No-Threshold (LNT) Hypothesis

Edward J. Calabrese<sup>a,1</sup> and Michael K. O'Connor<sup>b</sup>

<sup>a</sup> Department of Public Health, Environmental Health Sciences, University of Massachusetts, Amherst, Massachusetts 01003; and <sup>b</sup> Mayo Clinic, Section of Nuclear Medicine, Rochester, Minnesota 55905

---

Calabrese, E. J. and O'Connor, M. K. Estimating Risk of Low Radiation Doses – A Critical Review of the BEIR VII Report and its Use of the Linear No-Threshold (LNT) Hypothesis. *Radiat. Res.* **182**, 463–474 (2014).

This article explores the origin of the linear no-threshold (LNT) dose-response model and how it came to be used in cancer risk assessment worldwide. Following this historical appraisal is an evaluation of the LNT model, within the framework of the BEIR VII report of the National Academy of Sciences, on the health effects of ionizing radiation. The final section of this article provides an assessment of the LNT model's capacity to make accurate predictions of risk in the low-dose zone based on recent molecular mechanistic findings and epidemiological methods, with particular emphasis on the limitations of epidemiological studies to estimate risks in the low-dose zone. © 2014 by Radiation Research Society

---

### INTRODUCTION

In the U.S., it is well recognized that the increasing use of diagnostic imaging procedures over the last two decades has led to a significant increase in the collective radiation dose to the public (1). This increased dose has generated concern among the public and regulatory authorities and has been fueled in no small part by numerous scientific articles claiming that this increase will result in tens of thousands of excess cancer occurrences per year (2–4). These estimates of excess cancers are underpinned by one key document, the BEIR VII report (5) (or one of its predecessors), which itself has as its foundation the use of the linear no-threshold (LNT) dose-response model. The LNT model is used to estimate cancer risks from exposures to low doses of ionizing radiation and chemical carcinogens. Thus, in examining how estimates of cancer fatalities are obtained

it is important to understand the origins, strengths and limitations of both the BEIR VII report and the LNT model on which it is based. Around the time that the BEIR VII report was published, the French Academy of Sciences also published a comparable evaluation of carcinogenic risks of ionizing radiation. The French Academy report emphasized the significance of low-dose induced adaptive responses and came to a very different conclusion than the BEIR VII report, and suggested that extrapolation from high to low doses could not be reliably done, thereby challenging an LNT model use in cancer risk assessment (6).

### LNT MODEL AND BEIR: HISTORICAL FOUNDATIONS

About a year after Muller's 1927 report (7) that X rays could induce mutations in the germ cells of male fruit flies, two University of California physical chemists, Olson and Lewis, proposed the LNT model (8) to account for genetic changes in the genome from background ionizing radiation, thereby offering a mechanistic explanation of Darwin's theory of evolution. This LNT mutational explanation from cosmic/background radiation as the driver of evolutionary change was soon widely rejected (9) and remains so to this day since mutational changes in multiple experimental models were not effectively produced even at radiation doses several orders of magnitude greater than background radiation (10).

Despite the inability of background ionizing radiation to induce ostensible mutational changes in these studies, the LNT model was adopted by Hermann J. Muller and the radiation genetics community in an attempt to predict the effects of ionizing radiation on the genome (11, 12). They theorized various hit scenarios, developed mathematical equations to describe theoretical mutational responses and then matched their predictions to the mutation data of Muller and other researchers. Linear dose responses at very high doses, several hundred thousand-fold greater than background, visually matched their single hit model. As a

<sup>1</sup> Address for correspondence: Department of Public Health, Environmental Health Sciences, University of Massachusetts, Amherst, Massachusetts 01003; e-mail: edwardc@schoolph.umass.edu.

result of this convergence of the LNT model and high-dose data, these researchers linked the single-hit concept with the earlier LNT model, and gave the LNT a mechanism, even if ill-defined (13). Thus, the LNT model was reintroduced even though the original reason for its rejection (i.e., failure to detect mutations at low doses) was still valid.

Muller and his radiation geneticist colleagues worked over the next two decades to get major national and international committees to drop their historical reliance on a threshold dose-response model and to adopt the LNT single-hit model for risk assessment (14, 15). Even though they repeatedly failed in this effort, they finally achieved a long desired success when in 1955 the National Academy of Sciences (NAS) established the first committee on the Biological Effects of Atomic Radiation (BEAR), comprised of 12 radiation geneticists, including Muller, who persuaded the committee to adopt the LNT model for risk estimation (16). After the first two BEAR reports, in 1956 and 1960, the committee was essentially reformulated as the Biological Effects of Ionizing Radiation (BEIR) Committee. Subsequent BEIR reports up to and including the BEIR VII report continued to use the LNT model or variations thereof as the cornerstone for risk assessment. Given the prestige of the National Academy of Sciences, the recommendation to use the LNT model was adopted quickly in the U.S. and elsewhere, and generalized from the narrow area of genome risk to those involving somatic cells, with application to cancer risk assessment. When the U.S. Environmental Protection Agency (EPA) cancer risk policy was first developed in 1976, the EPA turned to the NAS for a suitable model for risk assessment and subsequently adopted the LNT model as its centerpiece for its cancer risk policy, providing the key foundation for cancer risk assessment guidelines starting in 1977, and continuing to the present day. Furthermore, the LNT model provides a fundamental underpinning for the Precautionary Principle that has captured regulatory agencies worldwide, which states that if an agent has a suspected risk of causing harm to the public, in the absence of scientific consensus that the agent is harmful, the burden of proof that it is not harmful falls on those overseeing the agent. In some legal systems, such as that of the European Union, the application of the precautionary principle has been made a statutory requirement in some areas of law.

### THE CASE FOR AND AGAINST THE LNT MODEL

A quick Google search of “radiation risks from medical procedures” returns approximately 22 million entries. A similar search on the risks of dying in an automobile accident (9 million hits) and smoking (23 million hits) are lower or comparable despite the daily reminder of deaths from auto accidents and volumes of scientific studies documenting the actual fatalities from smoking. By comparison, deaths from low doses of ionizing radiation

associated with medical imaging procedures are for the greater part hypothetical and unproven. So how as a society have we ended up in a position where the fear of ionizing radiation exceeds that of activities that cause measurable fatalities? David Ropeik contributed an interesting Op-Ed article in the *New York Times* (Oct 21, 2013) entitled “Fear vs. Radiation: The Mismatch”.<sup>2</sup> In it he discussed our fear of radiation, which stems from our understandable fear of the power of nuclear weapons. He added that “in the 68 years” since Hiroshima and Nagasaki, epidemiological and scientific studies have shown that at doses of less than 100 mSv, radiation causes no detectable elevations in normal rates of illness and disease. Yet, Ropeik states, “The robust evidence that ionizing radiation is a relatively low health risk dramatically contradicts common fears”.

In his historical review of the quarrels and arguments that consumed the members of the first BEAR Committee, Professor James Crow from the University of Wisconsin (17) concluded that while Muller did not have his way with much of the wording of the Committee report, his major practical recommendation nevertheless prevailed, which was that the standard be set low, in the vicinity of the natural background level. In the years immediately following the BEAR report there were numerous discussions among individuals and in committees, as well as Congressional hearings. Radiation protection became a major concern, resulting in an end to above-ground bomb testing, among other consequences. In the view of Professor Crow, Muller and the radiation geneticists certainly won the day. In retrospect many of the committee members, including Crow, oversold the dangers of radiation, and thus shoulder some of the blame for what now seems to be an irrational emphasis by some scientists, the press, the general public and the regulatory agencies on low-level radiation in comparison to other greater risks. Calabrese has argued that Muller misled the scientific community during his highly influential 1946 Nobel Prize lecture on the nature of the dose response in the low-dose zone, demanding a change to the LNT model while claiming there was no longer any justification to continue to use the threshold (11, 12, 15, 18, 19). He appears to have made these remarks with detailed knowledge that the most recent and convincing data (though still unpublished at that time) on the nature of the dose response supported a threshold model. These were data from a Manhattan Project funded study at the University of Rochester under the direction of Curt Stern, a project on which Muller was a consultant. Muller and Stern's insistence that the LNT model was valid led to the data from this project being reinterpreted and constrained to fit the theory (18, 20–22). Calabrese (12, 18, 23) has shown that Muller and Stern went to considerable lengths to ensure the establishment of the LNT, providing a classic example

<sup>2</sup> Ropeik D. Fear vs. Radiation: The Mismatch. *The New York Times*. 2013 Oct 21. ([www.nytimes.com/2013/10/22/opinion/fear-vs-radiation-the-mismatch.html](http://www.nytimes.com/2013/10/22/opinion/fear-vs-radiation-the-mismatch.html))

of where the ends (i.e., reduction in exposure) justified the means (i.e., data obfuscation and selective interpretation). Stern further promoted the LNT through key articles in the journal *Genetics* for which he was editor (21, 22). Stern also coauthored a key technical note in *Science* supporting the LNT model, but which was devoid of all methods and supporting data [detailed analyses in refs. (12, 17, 23)]. Although the missing data was to be presented in a later manuscript, which as it turned out, never happened. Muller's actions have also been recently reviewed by Kesavan (24) who found that he made selective citations in his Nobel Prize lecture to buttress the LNT model. For example, Muller cited several studies (13, 25, 26) that all used high doses and dose rates and found linearity. However, he did not cite or discuss other articles (27–30) that did not support linearity at lower doses and dose rates. From the above brief historical assessment, it can be appreciated that the scientific rigor associated with the validation of LNT was abandoned in the drive to protect the public from what the radiation genetics community saw as the dangers of ionizing radiation.

In recent years societal fears of ionizing radiation have been redirected from events such as Chernobyl and Fukushima (that while headline-grabbing, have little impact on our daily lives), to now focus instead on medical imaging procedures such as CT scans (3, 4). Our failure to help the public understand the relatively low health risks associated with radiation is now impacting our daily lives and the decisions that people make on whether or not to undergo recommended vital imaging procedures that can impact their well being. The precautionary principle works well only if the action associated with reducing or eliminating the agent has no harmful effects. The negative consequences of the precautionary principle (i.e., fear of radiation and the consequential failure to use medical imaging to enable early diagnosis of serious medical conditions) seem to have been lost in the rush to eliminate sources of radiation from our lives.

Several articles in the medical literature over the past few years have predicted thousands of cancers and cancer deaths annually in the U.S. population caused by radiation exposures from medical imaging (3, 4). These predictions are derived from risk estimates, published in the BEIR VII report (5). These risk estimates are speculative with wide confidence intervals, and are based on risk models generated from studies on subjects exposed to high levels of radiation, and then extrapolated to low doses using the LNT model for radiation risk. The weak scientific foundation for these estimates is rarely understood and appreciated by the medical or scientific community, and has not been adequately explained by the BEIR VII Committee. Despite the limitations and uncertainties of cancer estimates in the report, the committee chair, Richard R. Monson, associate dean for professional education and professor of epidemiology, Harvard School of Public Health, commenting at the time of its release, stated unequivocally, “The scientific research base shows that there is no threshold of

exposure below which low levels of ionizing radiation can be demonstrated to be harmless or beneficial”. The news report from the National Academy of Sciences further stated that the preponderance of evidence supported the LNT model and dismissed any possibility that the LNT model exaggerates adverse health effects. It further stated, “Living at low altitudes, where there is less cosmic radiation, and living and working on the upper floors of buildings, where there is less radon gas – a primary source of natural ionizing radiation – are factors that could decrease exposure” and presumably, the associated risks (31). With such dogmatic statements, it should be no surprise that the general public continues to have an irrational fear of ionizing radiation.

It should be noted that the decisions made by the various BEIR Committees are often at odds with those from prior BEIR Committees and may well change with the next iteration of the BEIR process. For example, a review of earlier BEIR reports shows that modest changes in some of the hypotheses used to generate risk estimates can have dramatic consequences. Lifetime excess cancer risks estimated from BEIR III (32) and BEIR V (33) increased by an order of magnitude as a result of a decision to switch from a linear-quadratic risk model to a linear risk model. For example, instantaneous exposure to 100 mGy in males was estimated to result in 42 deaths per 100,000 in the BEIR III report using the additive risk model. This estimate increased to 660 deaths per 100,000 in the BEIR V report [p. 176, Table 4-4 (33)]. Furthermore, while the BEIR III report utilized both an additive risk model and a relative risk model, the BEIR V concluded that only the relative risk model was valid. By the time BEIR VII came out, the committee had reversed direction and was now using a combination of the two models. While the underlying scientific data reviewed by these committees had obviously been updated, there was and is nothing in the published literature indicating that the risks from ionizing radiation are an order of magnitude greater than previously thought.

The next section briefly presents the key studies considered by the most recent BEIR VII Committee in its consideration of the risks associated with low doses of ionizing radiation, and its use of this data in estimating cancer risk from low levels of ionizing radiation. These are balanced against position statements from scientific organizations involved in the use of ionizing radiation, which comment on the dangers to society when hypothetical predictions are made about cancer risks.

#### SOURCES OF DATA OF STOCHASTIC EFFECTS OF IONIZING RADIATION

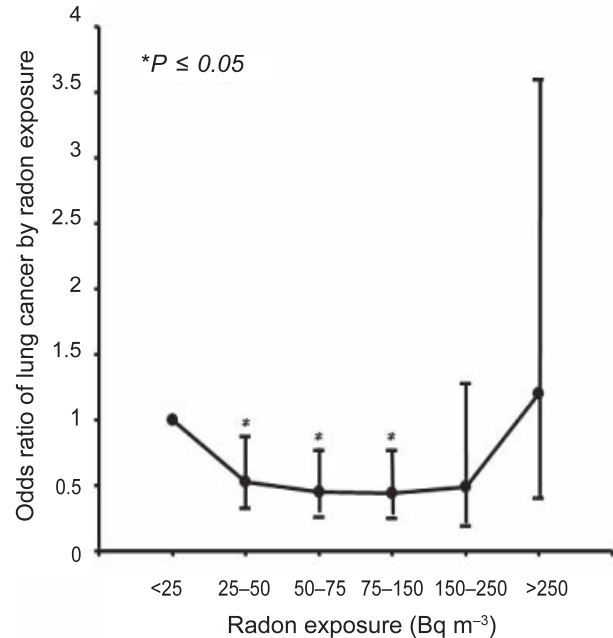
The BEIR VII Committee considered four primary sources of data on the stochastic effects of ionizing radiation. These were environmental radiation studies, occupational radiation studies, medical radiation studies and studies on the atomic bomb survivors. Below is a brief review of some of the key studies in each of these areas.

### Environmental Studies

Environmental studies included studies of populations living in areas of high natural background radiation, studies of populations exposed to fallout from nuclear accidents (Chernobyl) and populations living near nuclear power facilities. The largest study of populations living near nuclear facilities was that of Jablon *et al.* (34) and involved 1,800,000 cancer deaths between 1950–1984 in 107 counties in the U.S. The incidence of death due to leukemia or other cancers was found to be no more frequent in the study counties than in the control counties. In fact, the relative risk of leukemia dropped after the startup of the nuclear facilities. However, because the study was limited by the correlational approach and the large size of the geographic areas (counties) used, it could not prove the absence of a small effect and was considered unsuitable for risk estimation.

There were four studies of populations exposed to high natural background radiation. In all cases, no increased cancer risk was associated with any of the studies. On the contrary, some showed a radioprotective effect at higher background levels. Tao *et al.* (35) performed a 20 year study of over 125,000 subjects living in an area of high natural background radiation in Yangjiang, China. Risk estimates were negative (i.e., radioprotective effect), although this did not reach statistical significance. Studies from Chernobyl have focused primarily on thyroid cancer where there was a high radiation dose to many adults and children. Apart from the increased incidence of thyroid cancer, the BEIR VII report concluded that "...there is no evidence of an increase in any solid cancer type to date" [p. 228 (5)]. Because most environmental studies are descriptive in nature and ecologic in design, they were considered of limited use by the BEIR VII Committee in defining risk of disease in relationship to radiation exposure or dose and largely dismissed from further consideration.

One of the most interesting areas of research on environmental radiation has been radon exposure. A controversial study by Cohen in the late 1990s (36, 37) showed a beneficial effect of low levels of radon. The BEIR VI report (38) reviewed these and other ecologic studies and issued a strong judgment: They are not "informative" because of "inherent limitations of the ecologic method" and the latest BEIR VII report does not review or discuss radon exposure. A more recent report by Thompson *et al.* (39) describes a rigorous case-control study of lung cancer incidence versus residential radon exposure in Worcester County, Massachusetts, carried out between 1990–1999 with both cases and controls from a single health maintenance organization. Each case was matched individually by age and sex to two controls. Figure 1 shows the adjusted odds ratio of lung cancer as a function of radon concentration in the home. The authors concluded that the possibility of a hormetic effect on lung cancer at low radiation doses cannot be excluded. This would run contrary

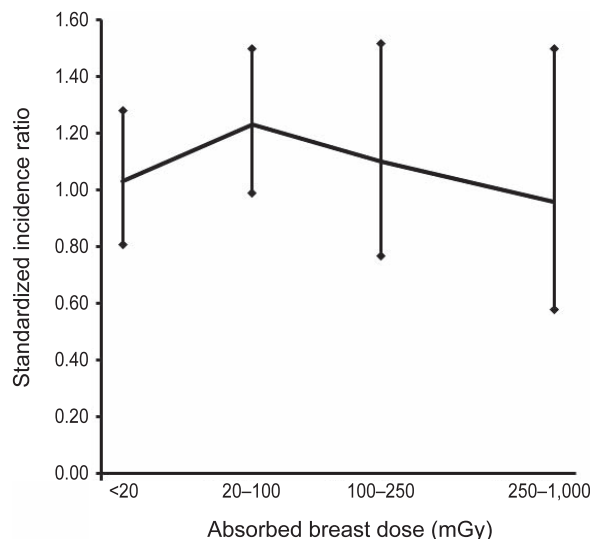


**FIG. 1.** The odds ratio (95% confidence interval) of lung cancer as a function of radon concentration in the home. Adapted from Table 2, Thompson *et al.* (39). Note that the EPA remediation standard of 4pCi/L (i.e., 148 Bq m<sup>-3</sup>) is in the radio protection (i.e., hormetic) zone.

to the recommendation from the National Academy of Science news report of BEIR VII to consider "living and working on the upper floors of buildings, where there is less radon gas" (31).

### Occupational Radiation Studies

The largest and most studied group of occupationally exposed workers is that in the nuclear power industry. Most of these workers receive low levels of external radiation (X rays and gamma rays). The most prominent report was from the 15-country collaborative study of over 400,000 nuclear industry workers in 154 facilities (40). The study showed a statistically significant increase in the risk of mortality from all cancers excluding leukemia in relationship to radiation exposure, with data from the Canadian sites being the chief driving force behind the worldwide results. Exclusion of the Canadian data resulted in a decrease in the risk of mortality from all cancers including leukemia. This led to a reanalysis of the Canadian data, which showed significant errors in dose reporting at one of their sites. After exclusion of data from that site, reanalysis of the data showed no increased cancer risk among any Canadian nuclear power plant workers and further showed lower rates of all causes of death and cancer mortality for this group than for the general Canadian population (41). As the BEIR VII report indicated, in most of the nuclear industry worker studies, rates for all causes and all cancer mortality in the workers were substantially lower than the reference population. The BEIR VII Committee did not attempt to ascertain why, but

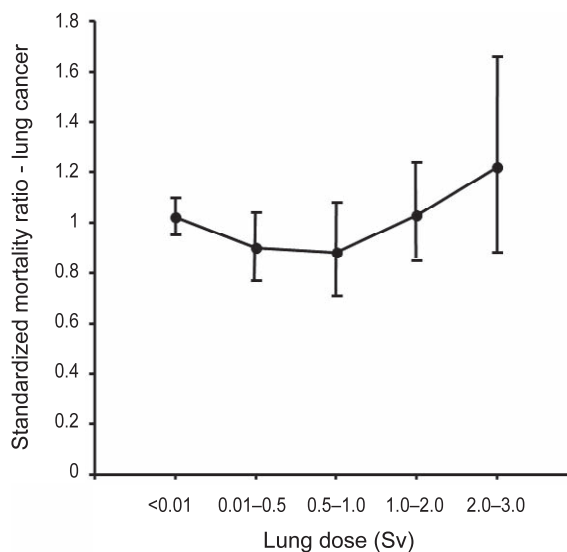


**FIG. 2.** Standardized incidence ratio for breast cancer as a function of absorbed breast dose. Mean follow-up years was 45. Adapted from Table 4, Lundell *et al.* (46).

speculated that it may be due to a “healthy worker effect and unknown differences between nuclear industry workers and the general public”. Consequently the BEIR VII Committee concluded that occupational studies were not suitable for the projection of population-based risks and eliminated them from further consideration in its risk estimates.

#### Medical Radiation Studies

Perhaps one of the most interesting study groups are the medical radiation study groups, since they are comprised of many subjects who are closest in ethnicity, lifestyle and diet to the general U.S. population, and therefore one would expect that cancer risk estimate from these studies would be most appropriate for use in risk estimates. The BEIR VII Committee looked at radiation risk for five types of malignancies (lung cancer, female breast cancer, thyroid cancer, leukemia and stomach cancer). The largest studies were those of Howe and Lundell (42–46). Lundell *et al.* (46) reported on the risk of breast cancer over a 45 year follow-up period after radiotherapy for skin hemangioma in over 17,000 infants. Howe and McLaughlin (42, 43) reported on the incidence of lung and breast cancer over a 40 year follow-up period after fluoroscopy in over 30,000 females aged 10–40 who were treated for tuberculosis. For most cancers observed after high doses, a linear model adequately described the relationship between dose and cancer incidence, however at low doses a very different pattern emerged. As shown here in Fig. 2 from Lundell *et al.* (46), no increased risk is observed out to exposures up to 500 mGy mean absorbed dose to the breast. Because of doses to the lungs and other organs, this is equivalent to an effective dose of >100 mSv. Figure 3 shows similar low

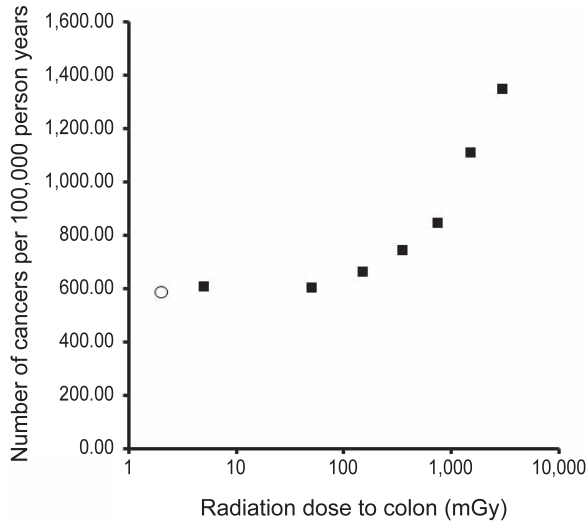


**FIG. 3.** Standardized mortality ratio for lung cancer as a function of absorbed dose to the lungs. Mean follow-up years was 30. Adapted from Table 3, Howe (42).

dose data on the relative risk of lung cancer from the studies of Howe (42). In both studies, there is no evidence of increased cancer risk at doses below 100 mSv.

#### Atomic Bomb Survivor Studies

The Life Span Study (LSS) cohort consists of approximately 120,000 survivors of the atomic bombings in Hiroshima and Nagasaki in 1945. This population has been extensively monitored since 1947 by the Radiation Effects Research Foundation (RERF) and its predecessor, the Atomic Bomb Casualty Commission, and continues to be monitored to this day. Published analysis of data on this cohort forms the basis for almost all risk estimates by the BEIR VII Committee. Unfortunately the BEIR VII report does not present the raw data from the LSS cohort, but instead relies on the risk estimates produced by researchers from the RERF. Indeed many of the published reports from the RERF do not provide the raw data, focusing instead on the various models used for risk estimates. The two most recent publications that provided useful raw data are Preston *et al.* (47) with analysis of 40 years of data from 1958–1998 and Ozasa *et al.* (48) with analysis of over 50 years of data from 1950–2003. Figure 4 plots the number of solid cancers at each radiation dose taken from Table 4 of Preston *et al.* (47) and adjusted to cancers per 100,000 people, with the weighted dose to the colon serving as a surrogate for effective whole-body dose. We have plotted the data on a semi-logarithmic scale to better show the results at low doses. The open circle in Fig. 4 represents the results for inhabitants of Hiroshima and Nagasaki who were not in the cities at the time of the bombings and hence can be assumed to have received none of the blast radiation. It can be seen in Fig. 4 that at doses up to ~100 mGy, no increase in the

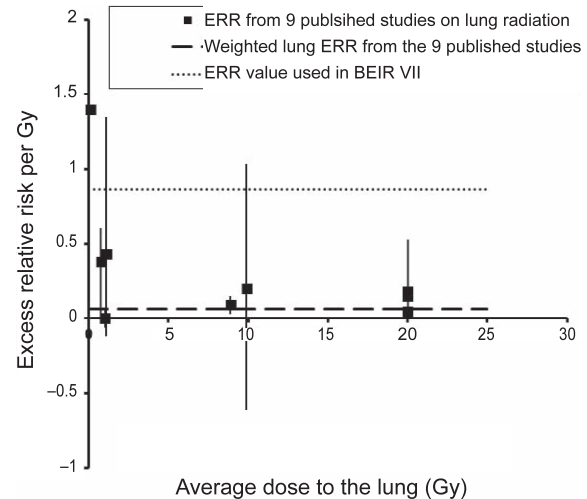


**FIG. 4.** Number of solid cancers per 100,000 person years as a function of radiation dose to the colon. Adapted from Table 4, Preston *et al.* (47). In this study, the weighted dose to the colon serving as a surrogate for effective whole body dose. Data point (○) = cancer incidence in inhabitants of Hiroshima and Nagasaki who were not in the city at the time of the bombing.

number of cancers is observed, and only at doses above that is a significant increase observed. In their analysis, Preston *et al.* (47) stated that “based on fitting a series of models with thresholds at the dose cut points. . . , the best estimate of a threshold was 0.04 Gy with an upper 90% confidence bound of about 0.085 Gy. However this model did not fit significantly better than a linear model”. A formal dose-threshold analysis performed on the more recent data reported by Ozasa *et al.* (48) indicated that a zero-dose threshold was the best estimate of a threshold dose, However Ozasa *et al.* found that the slope of the dose-response fit was higher at doses below 0.1 Gy than at higher doses, a finding that cannot be explained by the LNT model. Their analysis has been criticized for using a very restrictive model to fit the data (49). An analysis by Doss (50) using a more flexible model showed that the LSS data does not support a zero dose threshold and concluded that there was too much variability in the data to draw any conclusion as to the existence or absence of a threshold.

### RISK MODELS

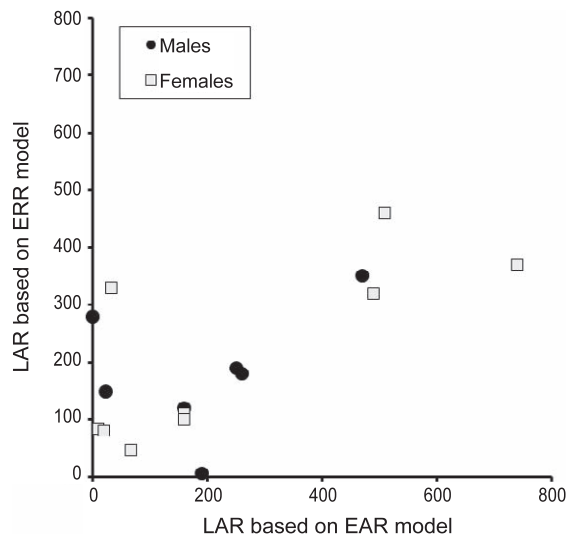
Even if we ignore the limitations of and arguments against the use of the LNT model and the lack of statistically sound data on the effects at low doses, there still remains the question of how to generate the appropriate risk models and factors to be used in estimating cancer risks at low doses. The BEIR VII Committee had at its disposal two competing risk models: the excess relative risk (ERR) model and the excess absolute risk (EAR) model. The ERR is the rate of disease in an exposed population divided by the rate of disease in an unexposed population, minus 1.0. This is a



**FIG. 5.** Distribution of study-specific estimates of ERR/Gy for lung cancer. Dashed line shows weight mean value of ERR for all studies. Dotted line is value of ERR used by BEIR VII. Adapted from Fig. 7-1, BEIR VII (5).

useful model if the population under investigation is similar to the population on which the model was based, so this would be an excellent model to predict cancer from ionizing radiation in a Japanese population living in wartime conditions. The EAR is the rate of disease in an exposed population minus the rate of disease in an unexposed population. This model is more suitable when there are significant differences (ethnicity, diet, etc.) between the population under investigation and that on which the model was based, and therefore would be better suited when extrapolating risk factors from the Japanese population at the time of the bombings to a U.S. population today. Thus, critical decisions to be made by the BEIR VII Committee included estimation of the values of ERR and EAR for each type of cancer and deciding which model to use and why. These models allow calculation of the risk of cancer at a given time after exposure and their value depends on the age and sex of the subject at the time of exposure. To calculate the lifetime risk of cancer from that exposure, a third model is employed called the lifetime attributable risk (LAR). The LAR is the difference in rate of a condition between the exposed population and an unexposed population. The LAR is an estimate of the probability of developing a premature cancer from radiation exposure over the life of the subject. Thus, it depends on the subject's age at the time of exposure and incorporates several additional factors such as latency period from exposure to first risk of cancer, and the dose and dose rate effectiveness factor, which is discussed in more detail below.

To illustrate the difficulty in calculating the ERR or EAR, consider Fig. 5, which shows values of ERR for lung cancer and is redrawn from Fig. 7-1 in the BEIR VII report [p. 175 (5)]. Each point on the graph represents one of nine studies of lung cancer evaluated by the BEIR Committee and



**FIG. 6.** Relationship between the Lifetime Attributable Risk (LAR) of solid cancer incidence estimated using the EAR and ERR risk models. LAR values are number of cancers per 100,000 persons exposed to 100 mGy. Adapted from Table 12-5A, BEIR VII (5).

considered acceptable for use in risk estimation. The graph plots the average dose to patients in each of the nine studies against the estimated value of ERR from each study. Ideally all estimates should be identical and should all lie within one or two standard deviations of each other. The estimates range from ERR = 0.0/Gy (i.e., no risk associated with ionizing radiation) to 1.4/Gy. A weighted mean, based on number of cancers in each study, yielded a risk coefficient of ERR = 0.05/Gy. Demonstrating its strong reliance on the RERF studies, the BEIR VII Committee chose a value of ERR = 0.86/Gy, which is 17 times larger than the weighted mean from all nine medical studies. A similar scenario played out in calculating the ERR for other cancers.

This factor of 17 difference in risk coefficient between the atomic bomb survivor studies and the medical radiation studies illustrates the tremendous uncertainties in estimating the risk factor for a single organ and the dangers in making any risk estimate based on this data. One can now repeat this process and model the data using the EAR model. Given that both models are essentially based on the RERF studies, one would expect reasonable agreement between the models for most cancers. Unfortunately that is not the case. Figure 6 shows the correlation (or lack thereof) between the LAR calculated using the EAR and ERR models based on data presented in Table 12-5A of the BEIR VII report [p. 279 (5)]. Each data point represents a different cancer for males and females. For some organs there is good agreement. For example, the LAR for bladder cancer in males is 160 based on the ERR model and 120 based on the EAR model. By comparison, the LAR for stomach cancer in females is 32 based on the ERR model and 330 based on the EAR model, a risk estimate 10 times greater. Given the lack of any significant correlation between the ERR and EAR

models, the committee opted to create a final risk model in the form:

Final Risk model =  $x \cdot \text{ERR} + (1 - x) \cdot \text{EAR}$ , where the factor  $x$  was determined subjectively by the committee. In the BEIR VII report this range of plausible values for LAR for each type of cancer was labeled a “subjective confidence interval” to emphasize its dependence on opinions in addition to direct numerical observation [p. 278 (5)]. Furthermore, the BEIR VII Committee went on to state that “because of the various sources of uncertainty it is important to regard specific estimates of LAR with a healthy skepticism, placing more faith in a range of possible values” [p. 278 (5)].

One additional factor that is built into the estimation of radiation risk in the BEIR VII report is the dose and dose rate effectiveness factor (DDREF). The DDREF is a factor applied to the LNT model that modifies (reduces) the dose-risk relationship estimated by the model to account for the level of the dose and the rate at which the dose is delivered (i.e., the value for the LAR is divided by the DDREF). The BEIR VII Committee chose a value of 2 for the DDREF. However, use of any value of the DDREF greater than 1 essentially converts the LNT into a linear-quadratic or biphasic model, and provides a means of modifying the linear model without officially abandoning the LNT hypothesis. The BEIR VII Committee did not define low dose and low dose rate, although this is generally accepted to mean cumulative doses less than 200 mGy, which would encompass all medical imaging procedures and background radiation (51). Values of the DDREF derived from a wide range of biological end points range from 1–35 (52) but are more generally accepted to be in the range from 2–10 (33) and suggest the need to have a larger DDREF for adequate and appropriate radiation protection after exposure to low-dose-rate radiation exposures. However, any value of DDREF greater than 5–10 would essentially negate the validity of the LNT and move closer to a threshold model. Since the publication of the BEIR VII report, extensive research in low-dose radiation has shown that the LNT model most likely overestimates the real risk of ionizing radiation at low doses and dose rates (53).

#### AAPM/HPS/UNSCEAR/ICRP/IOMP POLICY STATEMENTS

Many of the limitations of the BEIR VII report are buried deep within this 400-page document. As a consequence, many investigators, clinicians and scientists resort to the summary information presented in the Chapter 12 annexes rather than delve through the main document, and hence fail to appreciate the scientific weakness of the risk estimates generated therein. In particular, Annex 12D of the report provides users with a simple and easy-to-use chart that enables one to calculate the lifetime risk of cancer incidence and mortality for a given amount of radiation and for a



given age of exposure. This chart contains neither confidence intervals nor any message about the myriad of assumptions that went into the creation of these tables. It is partly because of the inappropriate use of these tables that many national and international organizations have issued statements denouncing the practice of multiplying small hypothetical risk estimates by large populations leading to highly speculative claims of the numbers of cancer deaths resulting from medical imaging. In 2011, both the Health Physics Society and the American Association of Physicists in Medicine issued the following position statements (54).

“The Health Physics Society recommends against quantitative estimation of health risks below an individual dose of 5 rem (50 mSv) in one year, or a lifetime dose of 10 rem (100 mSv), above that received from natural sources. For doses below 5–10 rem (50–100 mSv) risks of health effects are either too small to be observed or are nonexistent.”

The AAPM statement included the following: “Risks of medical imaging at patient doses below 50 mSv for single procedures or 100 mSv for multiple procedures over short time periods are too low to be detectable and may be nonexistent. Predictions of hypothetical cancer incidence and deaths in patient populations exposed to such low doses are highly speculative and should be discouraged. These predictions are harmful because they lead to sensationalistic articles in the public media that cause some patients and parents to refuse medical imaging procedures, placing them at substantial risk by not receiving the clinical benefits of the prescribed procedures.”

In addition, most recently UNSCEAR issued the following statement: “In general, increases in the incidence of health effects in populations cannot be attributed reliably to chronic exposure to radiation at levels that are typical of the global average background levels of radiation. This is because of the uncertainties associated with the assessment of risks at low doses, the current absence of radiation-specific biomarkers for health effects and the insufficient statistical power of epidemiological studies. Therefore, the Scientific Committee does not recommend multiplying very low doses by large numbers of individuals to estimate numbers of radiation-induced health effects within a population exposed to incremental doses at levels equivalent to or lower than natural background levels.” For reference, UNSCEAR has defined worldwide background as between 2–13 mSv/year (55).

## LNT MODEL IN PERSPECTIVE

### *Mechanistic Challenges to LNT-Hit Model*

Of significance, is that in the decades following the creation of the LNT single-hit dose response model based on radiation target theory, a series of progressive scientific discoveries have challenged its foundations (6). First, it

became recognized early on that multiple biological processes could produce linear relationships that did not involve a single-hit process (56–58). Second, many adverse effects of ionizing radiation were found to be mediated by hydroxyl radicals that were formed through the hydrolysis of water. Such chemical entities would need to migrate to biological targets and be subject to thermodynamic reaction principles requiring large numbers of molecules to affect a mutational event (59–61). Third, numerous cell types were observed to efficiently repair DNA that had been mutated (62). Fourth, prior low doses of mutagens, including ionizing radiation and chemicals, were subsequently reported to induce adaptive responses that markedly reduced the mutagenic effects of subsequent more massive exposures (63, 64), however, radiation target theory assumed that each dose was additive. Furthermore, hormetic-like biphasic dose responses have been widely reported for numerous end points, including mutations, cell transformation and cancer incidence for ionizing radiation and chemical carcinogens. In fact, many thousands of hormetic studies have been reported in the peer-reviewed literature, challenging not only the generality of the LNT concept but also its application to low-dose settings (65–67). Finally, apoptosis was discovered and then viewed within a mutational and cancer framework. It is not uncommon for damaged cells to be selected for destruction, again affecting predictions of the LNT model (68–70). In addition to the above, many other dose-dependent adaptive responses have emerged, further challenging the LNT model. For example, large scale toxicology studies often display hormetic dose responses for both ionizing radiation and chemical carcinogens. These studies included the massive FDA-funded mega-mouse study with 24,000 animals (71), as well as detailed reinvestigations of the effects of DDT on the rat model upon which regulatory-based risk assessments were made (72, 73). Multiple animal studies also revealed that low doses of ionizing radiation can significantly extend the lifespan of various mammalian models (74, 75). Reactive oxygen species, initially seen as a vehicle that mediated chemical and ionizing radiation adverse effects, are now viewed as also having critical cellular messaging functions involved in mechanisms by which low doses of ionizing radiation appear to extend life in a number of experimental animal models (76).

The LNT single-hit concept has also been challenged by proposals of other cancer risk models such as the multistage model. The LNT model predicted that a single alteration of DNA could initiate the process of carcinogenesis, and that once initiated, this process was irreversible. However, this assumption has been consistently shown to be false (77). In one such study Driver *et al.* (78) demonstrated that a single administration of the mutagen/carcinogen dimethylnitrosamine (DMN) induced a linear dose response for renal mesenchymal DNA adducts (early cancer process stage), as well as for mesenchymal foci (later cancer process stage), observations consistent with the LNT model. However, the

linear transition to the occurrence of tumor formation was not observed because the foci at the lower doses failed to proceed to the tumor stage, yielding a threshold, rather than a linear dose-response relationship (Fig. 7). Such dose-time response findings are more consistent with the concept of cancer being a multistage process with repair activities occurring at the lower dose.

### Regulatory Issues and LNT

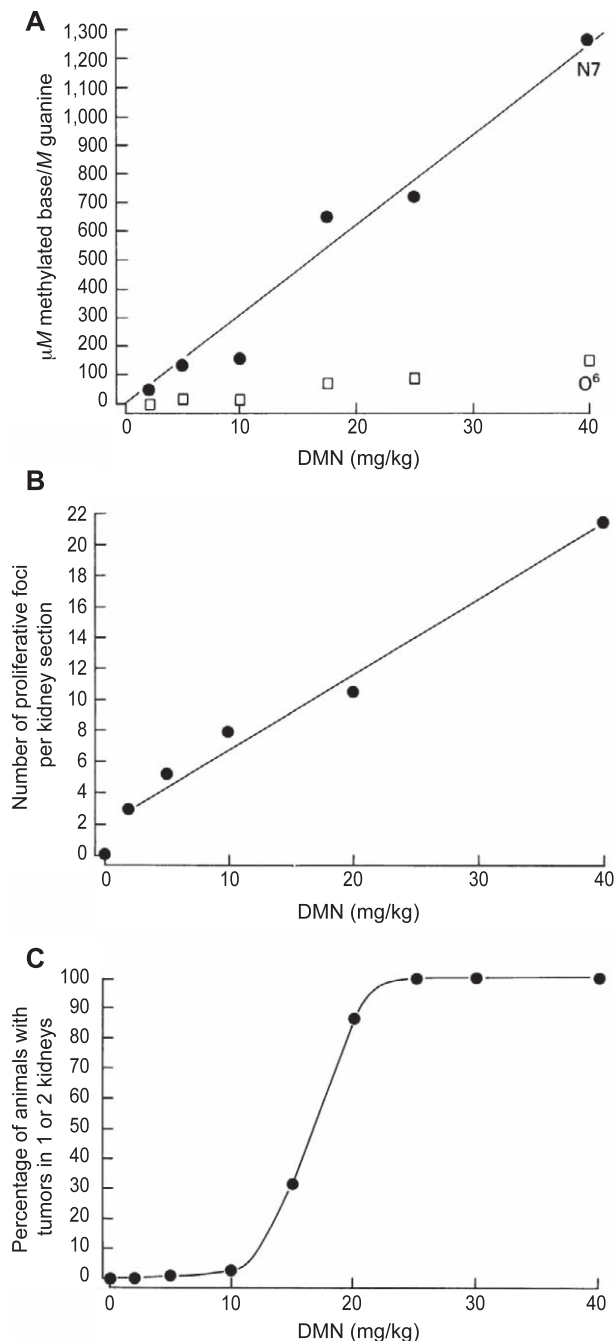
An evaluation of all EPA drinking water standards, including those for carcinogens and noncarcinogens, reveals that acceptable levels of exposure are in the range of  $10^{12}$ – $10^{20}$  molecules/liter. The EPA assumes that adult humans ingest two liters per day for a lifetime. This translates into  $>10^{24}$  molecules ingested per lifetime without noticeable effect. Since carcinogens at these “acceptable yet numerically massive” doses are expected to have negligible consequences, it reveals an LNT perspective without conceivable theoretical clinical and public health impact.

The adoption of the LNT for generalized use by regulatory agencies such as the EPA was linked with the belief that most human cancer was due to environmental agents. In his historical review of carcinogen regulation, Roy Albert (79), chair of the EPA’s Carcinogen Assessment Group (CAG), stated that carcinogen risk assessment effort was no less than an attempt by the Federal Government to prevent or greatly reduce cancer in the U.S., with its burden of some half-million deaths per year, by the regulatory control of carcinogens in the general environment.

Despite the fact that most industrialized countries such as the U.S. would be immensely impacted by the social, political and economic implications of the LNT and nagging “reality checks” that challenged the LNT that were ignored by the legislative, regulatory and scientific communities. For example, the number of liver cancers in the U.S. reported in 1980 was about 7,500 per year. Yet, the LNT model estimated that the number of liver cancer cases should have been in excess of 150,000 per year just from normal exposure to only three chemical carcinogens, not including the effects of ethanol, viruses and genetic predispositions (80). However, even with this and numerous other such inconsistencies the regulatory community has refused to confront the possibility that their decisions were grossly in error.

### Lack of Epidemiological Validation of LNT

Numerous epidemiological studies have been used to support LNT, threshold and hormetic dose responses. However, there are often many limitations with epidemiological studies that preclude obtaining reproducible findings in the low-dose zone, a point that is emphasized in the article “The Limits of Epidemiology” by Taubes and Mann (81) and in the published article of Professor John Ioannidis (82) at Stanford School of Medicine. Human variability can be extensive, and exposure assessment is often limited and



**FIG. 7.** Dose response for DMN: panel A: renal adducts; panel B: renal foci; panel C: renal tumors. Source: Driver *et al.* (78).

partially inaccurate. In addition, there is the complicating issue of competing causes of death, which can lead to invalid conclusions. Much greater clarity emerges when epidemiological odds ratios exceed two- to threefold. In fact, in the U.S. legal system one cannot usually claim causality until the risks from epidemiological studies have at least doubled (83). Yet, in the case of environmental regulation one talks about risks that may be indistinguishable from background or nearly so, as is often seen in epidemiological studies of particulate matter. Thus, as

valuable as human population studies are, there is little likelihood that epidemiological studies have the capacity to validate and/or test LNT predictions in the low-dose/risk zone. To better understand the nature of the dose response in the low-dose zone it is necessary to use biological models with low variability, high reproducibility and where mechanistic follow-up is practical. This is why the emphasis on assessing the occurrence of hormetic dose responses in the Hormesis Database involves cell model and whole animal studies (84, 85).

#### *Individual Versus Population-Based Thresholds*

It has been argued that while there may be thresholds for individuals there are no thresholds for populations, since humans display such widespread genetic, social, behavioral and cultural heterogeneity. While there can be significant inter-individual variability in response to toxic substances suggesting support for a population-based LNT model perspective, this argument fails to be useful in the LNT debate. Since people are typically exposed to greater than  $10^{24}$  molecules of individual regulated carcinogens at *de minimus* risk levels ( $<10^{-6}$  lifetime cancer risk), even adding a 100–1,000 greater response sensitivity in a group at high risk would mean that such dose levels are still without notable effect (86). That is, even populations have thresholds.

### CONCLUSION

We contend that the decision to accept the LNT model was based on a flawed scientific foundation. It was promoted through a series of highly biased representations of the data by leading radiation geneticists in the 1940s and 1950s. These geneticists convinced their colleagues on key committees such as the United States National Academy of Sciences BEAR I Genetics Panel in 1956 to switch from the threshold to the LNT for genomic risk assessment.

The main source of data for the BEIR VII risk estimates was obtained from the survivors of the Japanese A-bomb explosions, a population greatly different from the U.S. population that was exposed to radiation conditions greatly different from those of medical imaging. Even so, data from the Japanese studies frequently reveal a threshold dose for increased cancers in the irradiated populations. Collectively, the uncertainties in the derivation of the BEIR VII risk estimates, and the intrinsic speculative nature of the risk estimates themselves, cause predictions of cancers and cancer deaths to be more hypothetical than real in populations exposed to medical imaging. Several scientific organizations, including the Health Physics Society, American Association of Physicists in Medicine, the International Organization of Medical Physicists, the United Nations Scientific Committee on the Effects of Atomic Radiation and the International Commission on Radiological Protection, have warned against making such predic-

tions because of their speculative nature, supporting the conclusion that the risk projection model recommended in BEIR VII report should not be used for estimating cancer risks from low doses of radiation.

### ACKNOWLEDGMENT

Research activities in the area of dose response have been funded by the United States Air Force and ExxonMobil Foundation over a number of years. However, such funding support has not been used for the current article.

Received: June 12, 2014; accepted: August 28, 2014; published online: October 20, 2014

### REFERENCES

1. Ionizing radiation exposure of the population of the United States. NCRP Report No. 160. Bethesda: National Council on Radiation Protection and Measurements; 2009.
2. Brenner DJ, Elliston CD. Estimated radiation risks potentially associated with full-body CT screening. *Radiology* 2004; 232:225–9.
3. Smith-Bindman R, Lipson J, Marcus R, Kim KP, Mahesh M, Gould R, et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Arch Intern Med* 2009; 169:2078–86.
4. Berrington de González A, Mahesh M, Kim KP, Bhargavan M, Lewis R, Mettler F, et al. Projected cancer risks from computed tomographic scans performed in the United States in 2007. *Arch Intern Med* 2009; 169:2071–7.
5. NCR, Health risks from exposures to low levels of ionizing radiation: BEIR VII Phase 2. National Research Council, Washington DC: National Academy Press; 2006.
6. Tubiana M, Aurengo A, Auerbeck D, Bonnin A, LeGuen B, Masse R. Dose-effect relationships and estimation of the carcinogenic effect of low doses of ionizing radiation. Joint Report of the Academie des Sciences, Academie Nationale de Medecine: 2005.
7. Muller HJ. Artificial transmutation of the gene. *Science* 1927; 66:84–7.
8. Olson AR, Lewis GN. Natural reactivity and the origin of species. *Nature* 1928; 121:673–4.
9. Muller HJ, Mott-Smith LM. The frequency of translocations produced by x-rays in *Drosophila*. *Genetics* 1930; 15:283–331.
10. Giles N. Spontaneous chromosome aberrations in *Tradescantia*. *Genetics* 1940; 25:69–87.
11. Calabrese EJ. Origin of the linearity no threshold (LNT) dose-response concept. *Arch Toxicol* 2013; 87:1621–33.
12. Calabrese EJ. How the U.S. National Academy of Sciences misled the world community on cancer risk assessment: new findings challenge historical foundations of the linear dose response. *Arch Toxicol* 2013; 87:2063–81.
13. Timofeeff-Ressovsky NW, Zimmer KG, Delbruck M. *Über die Natur der Genmutation und der Genstruktur*. Nachrichten von der Gesellschaft der Wissenschaften zu Göttingen: Mathematische-Physikalische Klasse, Fachgruppe VI. *Biologie* 1935; 1:189–245.
14. Calabrese EJ. The road to linearity: why linearity at low doses became the basis for carcinogen risk assessment. *Arch Toxicol* 2009; 83:203–25.
15. Calabrese EJ. Toxicology rewrites its history and rethinks its future: giving equal focus to both harmful and beneficial effects. *Environ Toxicol Chem* 2011; 30:2658–73.
16. NAS/National Research Council. The biological effects of atomic radiation. A report to the public. Washington DC; 1956.

17. Crow JF. Quarreling geneticists and a diplomat. *Genetics* 1995; 140:421–6.
18. Calabrese EJ. Key studies to support cancer risk assessment questioned. *Environ Mol Mut* 2011; 52:595–606.
19. Calabrese EJ. Muller's Nobel Prize lecture: when ideology prevailed over science. *Toxicol Sci* 2012; 126:1–4.
20. Uphoff DE, Stern C. The genetic effects of low intensity irradiation. *Science* 1949; 109:609–10.
21. Caspari E, Stern C. The influence of chronic irradiation with gamma rays at low dosages on the mutation rate in *Drosophila melanogaster*. *Genetics* 1948; 33:75–95.
22. Spencer WP, Stern C. Experiments to test the validity of the linear R-dose/mutation at low dosage. *Genetics* 1948; 33:43–74.
23. Calabrese EJ. Response to letter of Ralph J. Cicerone and Kevin Crowley regarding "How the U.S. National Academy of Sciences misled the world community on cancer risk assessment: New findings challenge historical foundations of the linear dose response." *Arch Toxicol* 2014; 88:173–7.
24. Kesavan PC. Linear, no threshold model in low-dose radiobiology-ideology versus science. *Curr Sci* 2014; 107:46–53.
25. Oliver CP. The effect of varying the duration of X-ray treatment upon the frequency of mutation. *Science* 1930; 71:44–6.
26. Hanson FB, Heys F. Radium and lethal mutations in *Drosophila*; further evidence of the proportionality rule from the effects of equivalent doses differently applied. *Am Nat* 1932; 66:335–45.
27. Hanson FB, Heys F. An analysis of the effect of the different rays of radium in producing lethal mutations in *Drosophila*. *Am Nat* 1929; 63:201–13.
28. Weinstein A. The production of mutations and rearrangements of genes by X-rays. *Science* 1928; LXVII:376–7.
29. Stadler LJ. Some genetic effects of X-rays in plants. *J Hered* 1930; 21:3–19.
30. Serebrowsky AS, Dubinin NP. X-ray experiments with *Drosophila*. *J Hered* 1930; 21:259–65.
31. National Academies News Report. Low levels of ionizing radiation may cause harm. June 29, 2005. (<http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=11340>)
32. NRC, The effects on populations of exposure to low levels of ionizing radiation, BEIR III. National Research Council, Washington, DC: National Academy Press; 1980.
33. NRC, Health Effects of Exposure to Low Levels of ionizing radiation, BEIR V. National Research Council, Washington, DC: National Academy Press; 1990.
34. Jablon S, Hrubec Z, Boice JD. Cancer in populations living near nuclear facilities. A survey of mortality nationwide and incidence in two states. *JAMA* 1991; 265:1403–8.
35. Tao Z, Cha Y, Sun Q. Cancer mortality in high background radiation area of Yangjiang, China, 1979–1995. *Zhonghua Yi Xue Za Zhi*. 1999; 79:487–92.
36. Cohen BL. Test of the linear-no threshold theory of radiation carcinogenesis for inhaled radon decay products. *Health Phys* 1995; 68:157–74.
37. Cohen BL. Lung cancer rate vs. mean radon level in U.S. counties of various characteristics. *Health Phys* 1997; 72:114–9.
38. NRC, Health effects of exposure to radon, BEIR VI. National Research Council, Washington, DC: National Academy Press; 1999.
39. Thompson RE, Nelson DF, Popkin JH, Popkin Z. Case-control study of lung cancer risk from residential radon exposure in Worcester County, Massachusetts. *Health Phys* 2008; 94:228–41.
40. Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, et al. The 15-Country collaborative study of cancer risk among radiation workers in the nuclear industry: estimates of radiation-related cancer risks. *Radiat Res* 2007; 167:396–416.
41. CNSC, Verifying Canadian nuclear energy worker radiation risk: a reanalysis of cancer mortality in Canadian nuclear energy workers (1957–1994): Summary report. Minister of Public Works and Government Services Canada. Catalogue number CC172-65/2011E-PDF. ISBN 978-1-100-17760-1. Canadian Nuclear Safety Commission; 2011.
42. Howe GR. Lung cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with lung cancer mortality in the atomic bomb survivors study. *Radiat Res* 1995; 142:295–304.
43. Howe GR, McLaughlin J. Breast cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with breast cancer mortality in the atomic bomb survivors study. *Radiat Res* 1996; 145:694–707.
44. Lundell M, Mattsson A, Hakulinen T, Holm LE. Breast cancer after radiotherapy for skin hemangioma in infancy. *Radiat Res* 1996; 145:225–30.
45. Lundell M, Holm LE. Mortality from leukemia after irradiation in infancy for skin hemangioma. *Radiat Res* 1996; 145:595–601.
46. Lundell M, Mattsson A, Karlsson P, Holmberg E, Gustafsson A, Holm LE. Breast cancer risk after radiotherapy in infancy: a pooled analysis of two Swedish cohorts of 17,202 infants. *Radiat Res* 1999; 151:626–32.
47. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, et al. Solid cancer incidence in atomic bomb survivors: 1958–1998. *Radiat Res* 2007; 168:1–64.
48. Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, et al. Studies of the mortality of atomic bomb survivors, Report 14, 1950–2003: an overview of cancer and noncancer diseases. *Radiat Res* 2012; 177:229–43.
49. Doss M, Egleston BL, Litwin S. Comments on "Studies of the mortality of atomic bomb survivors, report 14, 1950–2003: an overview of cancer and noncancer diseases" (*Radiat Res* 177, 229–243, 2012). *Radiat Res* 2012; 178:244–5.
50. Doss M. Linear no-threshold model vs. radiation hormesis. *Dose Response* 2013; 11:480–97.
51. UNSCEAR, Sources and effects of ionizing radiation. New York: United Nations; 1993.
52. Dauer LT, Brooks AL, Hoel DG, Morgan WF, Stram D, Tran P. Review and evaluation of updated research on the health effects associated with low-dose ionizing radiation. *Radiat Prot Dosimet* 2010; 140:103–36.
53. Brooks AL, Dauer LT. Advances in radiation biology: effect on nuclear medicine. *Semin Nucl Med* 2014; 44:179–86.
54. Hendee WR, O'Connor MK. Radiation risks of medical imaging: separating fact from fantasy. *Radiology* 2012; 264:312–21.
55. UNSCEAR, Chapter II, Section 1(f) Attributing health effects to radiation exposure and inferring risks. Report of the United Nations Scientific Committee on the effects of atomic radiation - Fifty-ninth session, 21–25 May 2012, Supplement No. 46. New York: United Nations; 2012.
56. Zimmer KG. Ergebnisse und Grenzen der treffertheoretischen Deutung von strahlenbiologischen Dosis-Effekt-Kurven. *Biol Zentral* 1941; 63:78.
57. Haas FI, Clark JB, Wyss O, Stone WS. Mutations and mutagenic agents in bacteria. *Am Nat* 1950; 84:261–74.
58. Kimball RF. Genetic effects of radiation. *Ann Rev Nucl Sci* 1952; 1:479–94.
59. Collinson E, Dainton FS, Smith DR, Tazuke S. Evidence for unit negative charge on hydrogen atom formed by action of ionising radiation on aqueous systems. *Proc Chem Soc* 1962; 140–4.
60. Czapski G, Schwarz HA. The nature of the reducing radical in water radiolysis. *J Phys Chem* 1962; 66:471–9.
61. Weiss J. Radiochemistry of aqueous solutions. *Nature* 1944; 153:748–50.

62. Hanawalt PC. Evolution of concepts in DNA repair. *Environ Mol Mut* 1994; 23(suppl 24):78–85.
63. Samson L, Cairns J. New pathway for DNA-repair in *Escherichia coli*. *Nature* 1977; 267:281–3.
64. Olivieri G, Bodycote J, Wolff S. Adaptive response of human lymphocytes to low concentrations of radioactive thymidine. *Science* 1984; 223:594–7.
65. Calabrese EJ, Baldwin LA. Toxicology rethinks its central belief - hormesis demands a reappraisal of the way risks are assessed. *Nature* 2003; 421:691–2.
66. Calabrese EJ. Hormesis: why it is important to toxicology and toxicologists. *Environ Toxicol Chem* 2008; 27:1451–74.
67. Sanders CL. Radiation hormesis and the linear-no-threshold assumption. Heidelberg, Germany: Springer-Verlag; 2010.
68. Scott BR. Stochastic thresholds: a novel explanation of nonlinear dose-response relationships for stochastic radiobiological effects. *Dose Response* 2006; 3:547–67.
69. Scott BR. Low-dose radiation-induced protective process and implications for risk assessment, cancer prevention, and cancer therapy. *Dose Response* 2007; 5:131–49.
70. Scott BR. It's time for a new low-dose-radiation risk assessment paradigm one that acknowledges hormesis. *Dose Response* 2008; 6:333–51.
71. Bruce RD, Carlton WW, Ferber KH, Hughes DH, Quast JF, Salsburg DS, et al. Reexamination of the ED01 study why the society of toxicology became involved. *Fund Appl Toxicol* 1981; 1:26–128.
72. Fukushima S, Kinoshita A, Puatanachokchai R, Kushida M, Wanibuchi H, Morimura K. Hormesis and dose-response-mediated mechanisms in carcinogenesis: evidence for a threshold in carcinogenicity of non-genotoxic carcinogens. *Carcinogenesis* 2005; 26:1835–45.
73. Sukata T, Uwagawa S, Ozaki K, Ogawa M, Nishikawa T, Iwai S, et al. Detailed low-dose study of 1,1-bis(p-chlorophenyl)-2,2,2-trichloroethane carcinogenesis suggests the possibility of a hormetic effect. *Int J Cancer* 2002; 99:112–8.
74. Ina Y, Sakai K. Further study of prolongation of life span associated with immunological modification by chronic low-dose-rate irradiation in MRL-1pr/1pr mice: effects of whole-life irradiation. *Radiat Res* 2005; 163:418–23.
75. Ina Y, Tanooka H, Yamada T, Sakai K. Suppression of thymic lymphoma induction by lifelong low-dose-rate irradiation accompanied by immune activation in C57BL/6 mice. *Radiat Res* 2005; 63:153–8.
76. Ludovico P, Burhans WC. Reactive oxygen species, ageing and the hormesis police. *FEMS yeast research* 2013; 14:33–9.
77. Williams GM, Iatropoulos MJ, Jeffrey AM. Thresholds for DNA-reactive (genotoxic) organic carcinogens. *Toxicol Pathol* 2005; 18:69–77.
78. Driver HE, White IH, Butler WH. Dose-response relationships in chemical carcinogenesis: renal mesenchymal tumours induced in the rat by single dose dimethylnitrosamine. *Br J Exp Path* 1987; 68:133–43.
79. Albert RE. Carcinogen risk assessment in the U.S. environmental protection agency. *Crit Rev Toxicol* 1994; 24:75–85.
80. Calabrese EJ. Principles of animal extrapolation. New York: John Wiley and Sons, Inc; 1983.
81. Taubes G, Mann CC. Epidemiology faces its limits. *Science* 1995; 269:164–9.
82. Ioannidis JPA. Why most published research findings are false. *PLoS Med* 2005; 2:e124.
83. Carruth RS, Goldstein BD. Relative risk greater than two in proof of causation in toxic tort litigation. *Jurimetrics* 2001; 41:195–209.
84. Calabrese EJ, Blain R. The occurrence of hormetic dose responses in the toxicological literature, the hormesis database: an overview. *Toxicol Appl Pharm* 2005; 202:289–301.
85. Calabrese EJ, Blain R. The hormesis database: the occurrence of hormetic dose responses in the toxicological literature. *Reg Toxicol Pharm* 2011; 61:73–81.
86. Calabrese EJ. The dose-response: A fundamental concept in toxicology. In: AW Hayes, Editor. Principles and methods of toxicology, 6th ed. Boca Raton FL: CRC Press; 2014.