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Review

Ethical challenges of the linear non-threshold (LNT) cancer risk assessment revolution: History, insights, and lessons to be learned

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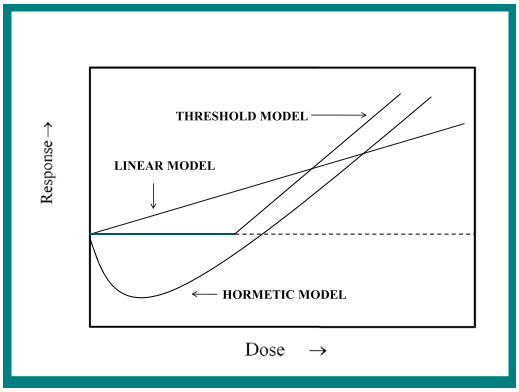
HIGHLIGHTS

- The LNT model has been the key model for cancer risk assessment.
- The LNT model lacks validation of its scientific foundations.
- The LNT has serious flaws that preclude accurate risk predictions.
- The LNT should not be used for cancer risk assessment.

GRAPHICAL ABSTRACT



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ABSTRACT

This paper provides historical review and evaluation of the development, adoption, and advocacy of the linear non-threshold (LNT) dose response model for cancer risk assessment as applied in practices and policies worldwide. It extends previous historical assessments and provides novel insights regarding: 1) how LNT bias became institutionalized in US governmental agencies, 2) how improper editorial practices at the journal *Science* promoted the adoption of LNT, 3) how a Nobel Prize winning scientist unjustifiably espoused and influenced support for replacing the threshold dose response model with the LNT model, 4) how the cover-up of striking and substantial experimental cancer data by US government scientists reduced support for the threshold dose response model at a critical period of cancer risk assessment policy adoption, and 5) how these events have negatively influenced cancer risk assessment practices and environmental and public health decisions for decades. These findings are presented to illustrate how profound and recognized mistakes, biases and unethical activities, inclusive of frank scientific misconduct, converged, and should motivate regulatory agencies worldwide to critically evaluate any existing policies that apply the LNT model as well as to serve as object lessons for current and future ethical conduct of research, and the provision of ethico-legal education in and across scientific curricula and institutions.

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Contents

1. Introduction

The linear non-threshold (LNT) dose response model has been the focus of considerable controversy in cancer risk assessment, especially in recent years. The controversy has been fueled by historical revelations that the scientific foundations of LNT were largely the product of methodological errors, profound personal and organizational bias, and overt scientific misconduct by radiation geneticists (Calabrese, 2015; Calabrese, 2019a, 2019b; Calabrese, 2020a, 2020b; Calabrese, 2021a, 2021b). Adding to the extensive historical evidence challenging the scientific basis of LNT, herein we present new informational developments that further clarify how the LNT concept became accepted, institutionalized and protected. In the main, we describe:

1. the institutionalization of US governmental bias for supporting LNT,
2. the historical influence of improper decisions by the editorial board of the journal *Science* that promoted wide acceptance of the LNT concept,
3. how a doctoral dissertation was used by Muller to reaffirm his gene mutation hypothesis and to criticize the threshold model, and the incorrect methods and procedural limitations that make those dissertation data "uninterpretable" and,
4. the intentional decision by leading US governmental researchers to not disclose the negative findings of a cancer study in mice that would have undermined support for LNT – both within the scientific community and crucial regulatory agencies.

The series of historical assessments of the LNT (Calabrese, 2011; Calabrese, 2013; Calabrese, 2015; Calabrese, 2017a, 2017b, 2017c; Calabrese, 2018a, 2018b; Calabrese, 2019a, 2019b; Calabrese, 2020a, 2020b; Calabrese, 2021a, 2021b), including those in the present paper, while challenging the integrity and foundations of cancer risk assessment, are provided in the scientific spirit (and obligation to remain) self-critical and self-revising, with hopes that this technical field and the regulatory agencies and policies overseeing its conduct will engage in requisite self-correction.

2. Institutional LNT bias in US agencies - historical development

The linear non-threshold (LNT) dose response model was adopted by the United States Environmental Protection Agency (EPA) in 1975 (Calabrese, 2019a). That decision was based on a recommendation by the US National Academies of Science (NAS) Biological Effects of Ionizing Radiation (BEIR) I Committee (National Academy of Sciences (NAS)/National Research Council (NRC), 1972) that depended heavily upon the extensive research of William L. Russell of Oak Ridge National Laboratory (ORNL) concerning the effects of ionizing radiation on mouse mutation rates. Of note is that those studies almost universally utilized the specific-locus test (SLT), which examines the origin of recessive mutations at seven genes. This LNT recommendation was applied to both genetic and cancer risks, and extended the groundbreaking report of the 1956 US NAS Biological Effects of Atomic Radiation (BEAR I) Genetics Panel that recommended changing the long-used threshold model to the LNT model for genetic risk assessment. The BEIR I (National Academy of Sciences (NAS)/National Research Council (NRC), 1972) recommendation would prove to be significant in that it represented the first time that a US NAS committee was created by a US governmental organization [i.e., the Federal Radiation Council (FRC)] to formally advise a governmental agency on the health risks of ionizing radiation. The previous BEAR Genetics Panels, which were active for nearly a decade (1955–1964), were created by the US NAS. However, they were fully supported by funding from the Rockefeller Foundation (RF). Of note is that the President of the NAS (Detlev Bronk) was also the President of the Rockefeller Institute for Medical Sciences (later the Rockefeller University), and a member of the RF Board of Directors. Soon after the new BEIR I committee was created in 1970, US President Richard Nixon instituted a major reorganization of environmental administrative and research activities, which led to the creation of the US EPA. In so doing, Nixon eliminated the FRC and transferred its functions and personnel to the EPA. Thus, BEIR I (National Academy of Sciences (NAS)/National Research Council (NRC), 1972) became a major advisory committee for the fledgling EPA, which in some important respects positioned BEIR I (National Academy of Sciences (NAS)/National Research Council (NRC), 1972) to influence in a major way the direction of EPA cancer policies.

The "new" EPA radiation health group essentially was comprised of personnel of FRC who had been transferred to a new administrative structure. The FRC itself was likewise created by the decision of President Dwight D. Eisenhower to remove the responsibility for radiation health risks from the US Atomic Energy Commission (AEC). During that period there were numerous above-ground tests of atomic weapons, principally by the US and the Soviet Union, but also by the United Kingdom and France. US testing began in 1951, just prior to when Eisenhower was elected President. Above-ground detonations of nuclear devices became a regular occurrence in the state of Nevada under the direction of the AEC, and created considerable public health and medical concerns within the scientific community, especially among radiation geneticists. By 1954, these activities prompted public confrontation between leaders of the radiation genetics community and other prominent scientists, such as Linus Pauling (the 1954 Nobel Prize recipient in Chemistry), and the AEC (Jolly, 2002). Central to the argument was the possibility for radiation-induced mutations, birth defects, and certain types of cancer, such as leukemia (Sturtevant, 1954, 1955). These issues became prominent in the US, and there were several challenges (e.g., actions of Linus Pauling and radiation geneticists such as Alfred Sturtevant) to the AEC leadership.

One of the fundamental concerns was the dose-response parameters and effects elicited by low dose radiation. The leadership of the AEC asserted that there was no need for public health concern about national fallout exposures, as post-detonation levels of environmental radiation were far below any threshold for harm (Strauss, 1954). In contrast, the radiation genetics community argued that the AEC was wrong and irresponsible, and they based their position upon the LNT model (Sturtevant, 1954; Calabrese, 2021a), which indicated the absence of any threshold level, and thus that any and all exposures were harmful.

The tension between the radiation genetics community and the Eisenhower administration increased during this period, and the administrator of the AEC bore the brunt of the criticism. Since the RF was funding many academic radiation geneticists, as well as Pauling's research, a convergence of these public criticisms emerged such that the politically powerful RF directly contacted Eisenhower to request that the NAS undertake a multi-dimensional assessment of all things nuclear – including issues of mutations induced in genes, which was highlighted in the request letter – with the RF offering to sponsor the activity (Rusk, 1955). The offer was accepted, and six scientific BEAR Panels were established in late 1955. The most visible group was the Genetics Panel, in that it was the only panel to make major headlines. The Genetics Panel was hand-picked by the RF, with all selected radiation geneticists being strong/ideological supporters of the LNT model (i.e., equivalent to a stacked jury). The radiation genetics community could offer their own perspective, distinct from a medical panel, where, as in the past, their views had typically been submerged and often rejected with respect to input and recommendations relevant to radiation-induced mutations and dose response (Calabrese, 2019a).

The Genetics Panel used its highly publicized 1956 report (National Academy of Sciences (NAS)/National Research Council (NRC), 1956) to both recommend the change from threshold to LNT models, and to also directly challenge the leadership and legitimacy of the AEC in the areas of public health policy and risk assessment, thereby negatively impacting the credibility of the AEC and markedly reducing its political support. Eisenhower eventually lost confidence in the AEC and eliminated its role in public health and risk assessment evaluation, transferring those functions to the new federal organization, the FRC. This was achieved by federal legislation signed by President Eisenhower in 1959. Yet, while there remains debate regarding whether the actual goals of the RF had been to achieve acceptance of LNT and to weaken the AEC, it cannot be denied that these ends were achieved efficiently and successfully.

The transfer of health risk assessment from the AEC to the newly-founded FRC represented a major organizational change that affected how risk(s) would be evaluated. Of profound significance is that the FRC quickly came to rely on the guidance of the National Committee on Radiation Protection (NCRP), an independent committee that had existed for nearly 30 years, and which had a strong historical affiliation with the US National Bureau of Standards (Walker, 2000). It is of practical importance that the NCRP used health advisory committees to direct policies and activities, and it is highly relevant that such committees in the 1950s contained radiation geneticists, such as Hermann Muller, Curt Stern, and others who strongly supported LNT, as members.

The FRC also invited key radiation geneticists to serve as their principal source of advice on risks from ionizing radiation, which, in effect, gave the same group of LNT supporters multiple vectors and opportunities to impugn the threshold model and lobby for its replacement by the LNT model. In fact, in its 1961 report (published in 1962) on risks from radioactive fallout, the FRC acknowledged the guidance of James Crow, James Neel, William Russell, and other members of the BEAR Genetics Panel, and asserted the belief that there was no safe exposure to ionizing radiation because there was no threshold for genetic mutations (Federal Radiation Council, 1962).

Eisenhower's removal of health risk assessment functions from the AEC resulted in a philosophical change that has altered the scientific basis of radiation-induced hereditary and overall cancer risk evaluations to the present time. While the scope of the FRC was, by statute, limited to radiation, the next major institutional change occurred when Nixon transferred the FRC staff and its functions to the EPA, thereby greatly expanding the Congressional mandate to apply to both radiation and chemical exposures across all environmental settings and media (i.e., air, water, soil). In this way, the radiation advisory project of the FRC, which was the creation of BEIR I, became an EPA project of transformational importance, despite the fact that this leverage was not recognized for its significance at the time.

The transfer of FRC personnel to the EPA also brought an institutional history that had supported LNT (in contrast to the risk assessment philosophy held by the AEC that primarily supported the idea of a threshold). This sustained the LNT philosophy as a prominent construct of BEIR I, and was certainly fortified by James Crow's chairing the genetics committee, along with several of the previous BEAR I Genetics Panel members. Likewise, Edward B. Lewis was on both the BEIR I oversight committee with Crow and on the epidemiological committee. The BEIR I Genetics Panel had a very powerful effect, as it made the recommendation to adopt LNT for risk assessment, led to the diminished influence of the AEC, and enabled placement of LNT-supporting radiation geneticists in key positions as advisors to FRC, and subsequently the EPA. In this way, the Panel assured the adoption of LNT, leading to its use to the present time.

3. Science: Muller's nobel prize paper lacked any data

In related fashion to the previous discussion, here we provide four instances in which editorial practices and decisions at *Science* significantly enhanced the broad acceptance of LNT. These instances include a report of the production of mutations by Muller (1927a); the key summary findings of the Manhattan Project about radiation-induced mutations (Uphoff and Stern, 1949); the recommendations of the LNT model by the BEAR I Genetics Panel (National Academy of Sciences (NAS)/National Research Council (NRC), 1956) and the paper by Edward B Lewis (1957) that utilized the LNT model in linking radiation and leukemia. These four examples are distributed in the paper according to their temporal period/context. A more detailed description and assessment of the role of *Science* in the promotion of LNT and its ethical issues are presented elsewhere (Calabrese and Giordano, 2022).

The LNT dose response theory was based upon initial work by Olson and Lewis (1928) proposing that background radiation was the underlying mechanism of evolution, and which was based on Muller's earlier (Muller, 1927a) gene mutation findings. Muller (1930) subsequently conceptualized the Proportionality Rule for ionizing radiation, applying it first to human genetic diseases and later to the pathogenesis of cancer.

On July 22, 1927, Muller announced that X-radiation was able to induce gene mutations in a paper published in *Science* entitled “Artificial Transmutation of the Gene”. The paper presented no data, but rather only a discussion of Muller's findings (i.e., transgenerational phenotypic changes) and his claim that tiny changes in the gene, which he called “point mutations”, could be radiation-induced. Thus, publication in *Science* did not involve peer review of Muller's data. Close examination of statements in the discussion section of Muller's *Science* paper suggests that he only discussed findings of the first of his three (Nobel Prize-winning) experiments. Muller finally presented his data in September 1927, at the 5th International Genetics Congress in Berlin. A manuscript, without a Methods section, Discussion or References, was published in the Congress Proceedings (Muller, 1928). Since no changes were made in the paper that was presented at the meeting (Muller, 1946a – letter to Altenburg, July 8, 1946), it is therefore likely that the work published in the conference proceedings was not peer reviewed. Thus, Muller's work achieved scholarly primacy in the research community while apparently being devoid of data or peer review. Hence, Muller achieved a profound competitive advantage over other researchers (e.g., Lewis J. Stadler) who were also close to publishing their work on radiation-induced gene mutation.

Muller was most likely able to manipulate the situation to his advantage since the *Science* editor was a long-time friend of his doctoral advisor at Columbia University, where both had been faculty members. The *Science* journal publication (viz. - without data) was cited extensively, while the conference paper was published in a poorly distributed proceedings,

which to date has only been rarely cited.[2] The considerable publicity that Muller received provided the necessary impetus – and defensibility – for LNT advocacy, based in large part upon his Proportionality Rule.

Muller repeatedly attempted to prove that he had induced gene mutation as skepticism toward his undocumented *Science* publication mounted. For example, he tried to demonstrate induced gene mutation using an indirect approach, seeking to prove the occurrence of "reverse mutations". However, this was unconvincing. Proof remained lacking after numerous efforts and two decades of attempts (Lefevre, 1949; Lefevre, 1950; Stadler, 1954; Nuffer, 1957). In fact, by 1956, some ten years after receiving the Nobel Prize for "producing gene mutations", Muller essentially abandoned his pursuit[3] and conceded that he actually had produced massive chromosome deletions and other chromosomal damages, rather than the point mutations he had originally claimed. The difference is highly significant to genetics and health risk assessment.

Later investigations, using nucleotide analyses, indeed confirmed that the doses Muller had employed in an attempt to induce gene mutations tended to evoke widespread gene deletions and other chromosomal damage (Ratner et al., 2001; Roman, 1988; Crow and Abrahamson, 1997; see Calabrese, 2019a, page 9, left column for numerous other supporting references).

Prior to any explicit discrediting of Muller's claims of gene mutation, a key paper by Timofeeff-Ressovsky et al. (1935) utilized target theory to propose the LNT single-hit model, and this work would have a prolonged influence on the field, and ultimately upon the adoption of LNT by regulatory agencies (e.g., EPA) some four decades later. The influence of the single-hit model was based upon its conceptualized integration of a non-repair-based target mechanism to support the uncorroborated dose-response reports of Muller and others (Ducoff, 2002). But it is important to note that the Timofeeff-Ressovsky approach was incorrectly formulated upon the idea that radiation was inducing point mutations in genes, which Muller continued to defend for years. In other words, it represented a prototypical illogical – and thus indefensible – argument, in that it was based upon incorrect premises, and therefore proposed unsupportable conclusions. Hence, Muller had confused an observation (chromosome damage) with a mechanism (mutagenesis), while the EPA would desire a simple and general solution that could be applied both to radiation and chemicals (Albert, 1994).

4. Muller misleads scientific community during Nobel Prize Lecture: his criticism of threshold dose response model is discredited due to flaws in dissertation

Despite his attempts to support the gene mutation hypothesis and to influence broad acceptance of the LNT model, Muller clearly was aware of the troubling issues in his scientific disputes with Stadler and others concerning the mutation mechanism. Muller subsequently adopted a new strategy to prove that X-rays induced gene mutations, and he began testing whether total dose or dose-rate would best predict mutation risk. This concept was furthered by doctoral dissertation studies of Ray-Chaudhuri at the University of Edinburgh from 1938 to 1939. Muller's standing made his work attractive to young researchers, and difficult for peers to openly criticize. This could be seen as exemplar of "association fallacy", in that the wide perception of Muller's professional status inferred the correctness of his speculations and claims.

Muller believed in a "piggy bank" dose response model of genetic damage, in which all genetic damage was cumulative, was irreversible, could not be repaired, and displayed a linear dose response to background and below background. Ray-Chaudhuri tested this model over a 120,000-fold dose rate range for X-ray induced mutation using the sex-linked recessive method in *Drosophila melanogaster* (i.e., the common fruit fly). Ray-Chaudhuri (1939, 1944) reported that his findings supported the total dose hypothesis. The results of testing over this extensive range of doses and dose rates led Muller to support both gene mutation and linearity interpretations at low doses, and to use Ray-Chaudhuris data to convince many in the scientific community that not only had he (i.e., Muller) induced gene mutations as previously claimed, but that his findings unequivocally supported the LNT model, and thereby discredited the threshold model. So confident was Muller that he announced this during his Nobel Prize Lecture, and in so doing asserted credibility to his position by using Ray-Chaudhuris results.

To be sure, Muller exhibited considerable scientific bravado. Moreover, the new elevated status afforded positional credibility and clout; after all, who would dare to challenge a Nobel Prize (1946) winner on his own terms? Yet, closer examination of the historical record suggests that Muller actually may not have been so confident. After he was hired by Curt Stern in 1943 to serve as a consultant on the Manhattan Project involving development of the atomic bomb, he convinced Stern to replicate the Ray-Chaudhuri project using lower doses. In this way, Muller tacitly inferred that all had not gone as well as was overtly asserted in Edinburgh (Muller, 1943 - letter to Stern).

Problems with the Ray-Chaudhuri dissertation started when the relatively inexperienced graduate student was directed by Muller to make homozygous strains via a series of genetic crosses (see Calabrese, 2020b, for a detailed review of the Ray-Chaudhuri research and citations for correspondence and related materials). Muller taught him the basics, but then left him on his own.[4] Ray-Chaudhuris contemporary correspondences reveal a struggling graduate student who was uncertain whether he could develop the necessary skills in time to properly execute the study. As a matter of fact, Ray-Chaudhuri himself admitted to failure in achieving the directed goal of creating homozygous *Drosophila*; and instead produced a mix of identifiable sub-strains that were differentially distributed in significantly variant proportions across control and treatment groups.

From its beginning, therefore, the Ray-Chaudhuri dissertation was plagued by significant problems, in that the introduction of a second variable (substrains) would most certainly confound – if not make impossible – scientifically valid conclusions. However, after Ray-Chaudhuris apparent plea for assistance in a detailed letter, Muller returned only in time to deal with the results, but not soon enough to correct problems so that the experiments could be properly conducted (Calabrese, 2020b). Problems with the dissertation did not end with the issue of multiple substrains, indeed that was merely the first of a number of mistakes, technological failures, and poor decisions, many of which have been documented (Calabrese, 2011, 2020b). These include – but are not limited to – a modest sample size, lack of information on lethal clusters, concerns regarding female sterility, sex ratios, the age of males, uncertain use of

[2] Muller reported in an October 26, 1927, letter to Demerec (1927b) that James Mckeen Cattell, who was the owner and editor of *Science* and *The American Naturalist*, asked him (i.e. Muller) to recommend excellent papers that were presented at the 5th International Genetics Congress (Berlin) in September 1927, that could be republished in *The American Naturalist*, thereby giving the papers profoundly greater visibility. Cattell indicated that he would republish any paper that Muller suggested. This letter is important for several reasons. First, it demonstrates that Muller had a close relationship with Cattell, the editor of *Science* who published his paper in *Science* in July 1927. Second, Muller did not arrange to have his conference publication with the data supporting his claims of X-ray induced gene mutation to be republished. Thus, the question must be raised as to why the often self-serving Muller would not have acted to have his major data paper republished in *The American Naturalist*.

[3] In 1956, Muller (1956a) was finally forced to admit that collective research with *Drosophila* indicated that a substantial proportion of what he originally referred to as "point mutations" were now seen as gross genetic deficiencies/deletions and other structural changes, supporting the long-standing position of Lewis J. Stadler. Muller (1956a) wrote that "there is no doubt that in X-rayed *Drosophila* also, at least when the irradiation is applied to condensed chromosome stages, such as those of spermatozoa, deficiencies as well as other demonstrable structural changes arise with much higher frequency relative to changes that appear to involve but one gene…." The statement must have been hard for Muller to write since it eroded his long-time position asserting the primacy of "point" mutations. In essence, even though it took 25 years, Stadler had won the dispute but Muller, nonetheless, won the Nobel, even though, in retrospect, undeserved.

[4] Soon after getting Ray-Chaudhuri started on his research, Muller left Edinburgh for a prolonged trip to the US via the Queen Mary to visit family, do job interviews, and to do research at Woods Hole in Massachusetts (Carlson, 1981). Based on letters written by Ray-Chaudhuri, it appears that Muller remained on vacation/travel well into the month of September, with no clear indication when he returned to Edinburgh. It appears that Muller was not present for most, if not all, of the experimentation described in the Ray-Chaudhuri dissertation.

mold suppression agents, inadequate temperature control, and complete lack of a control group in one experiment (due to refrigeration failure). Pilot studies to determine diet and temperature optimization, and other parameters vital to *Drosophila* survival and function, were inexplicably not conducted with the *Drosophila* strain to be tested. This was problematic because subsequent testing of the strain that was used could not be performed so as to concomitantly study both mutation and translocation. As this problem was recognized, dietary changes were made in an attempt to correct the problem, but they were ineffective. Instead, these dietary changes created other concerns which may have affected sperm retention/radiation exposure due to changes in female egg laying activity.

Subsequent experiments by Ray-Chaudhuri replaced the *Drosophila* strain he was using with one that had also not been evaluated in pilot work. The new strain showed greater susceptibility to induced mutation and a lower background mutation rate in controls than the original strain, thereby adding further obfuscation – and concerns – to the research and its results. Despite these changes in diet and the use of the new strain, all data were combined and uniformly analyzed. In addition, there were three experiments in the reproductive study that failed to yield progeny.

These types of problems can arise in dissertation research. They can – and should - be recognized by the doctoral mentor and corrected over time; however, such correction was not implemented by Ray-Chaudhuri. This was because Muller was largely absent during the experiments, leaving the inexperienced Ray-Chaudhuri to make numerous decisions on his own, which proved to be erroneous at key points. Furthermore, time was somewhat of the essence, given the onset of World War II, and with pressure being put on Muller to return to the US, and Ray-Chaudhuri to return to India. In sum, the dissertation research was rife with flaws in design and execution, and it produced data that were far too problematic to yield reliable conclusions. And yet the data were used.

Another serious, and perhaps overriding, concern about the Ray-Chaudhuri dissertation is its failure to report whether the control and radiation treatment groups, which were in separate incubators, were in the same room and adjacent to each other (e.g., as was the case with the Uphoff and Stern (1947) and Caspari and Stern (1948) studies at the University of Rochester during the Manhattan Project, with which Muller was very actively associated). In these later studies, gamma rays from the radium source had the potential to affect the nearby controls. To minimize this effect, lead shielding was installed between the control and treatment group incubators. Nevertheless, the control group received about 1% of the dose received by the treatment group, yielding a total dose above background of about 0.6 r, with dose rate being about 100-fold greater than background.

In the Ray-Chaudhuri studies, because of the vastly wider range of doses and dose rates being studied, any control group exposure could potentially have been far more extreme and uncertain than in the Uphoff and Stern, and Caspari and Stern experiments. Yet, no information was provided concerning where the control and treatments were located, about the potential for exposure from the radiation source, or about lead shielding. If the control and treatment groups were housed similarly to those in the Uphoff and Caspari studies, and, taking into consideration the significantly higher dose rates/total doses involved in the Ray-Chaudhuri experiments, it seems that the estimated exposure of the control group might have been as much as 24 r higher than normal background over the course of the 30-day study.

Because the control did not show an excess mutational response, it is possible that the controls were moved sufficiently far away to make any exposure too low to be consequential (i.e., with a detectable increase in mutations). However, if the situation was similar to the Uphoff and Caspari experiments, and if the control were exposed to an additional 24 r, the absence of increased mutations could have simply resulted from the additional dose (perhaps as high as 24 r) received by the control being below a threshold. The failure to explicate the experimental storage environments and conditions is undoubtedly problematic and renders Ray-Chaudhuris findings uninterpretable (with respect to the validity of a threshold). Despite this fundamental – and we believe evident - reporting failure, Muller (1946b) used the dissertation in his Nobel Prize lecture, as noted above, as grounds to fortify his own work and dismiss the threshold model.

These problems in experimental method and reporting were obscured in Ray-Chaudhuri's (1939, 1944) publications, only to be eventually revealed by examination of the actual dissertation, related correspondence, supplementary data records, written comments by his Ph.D. committee, and other related documents (Calabrese, 2020b). By not articulating the many flaws of the research, inclusive of failure to report non-supportive data, failing to note the occurrence and distribution of *Drosophila* substrains, the location(s) and environs of the control and treatment groups, and possible need for (and/or absence of) adequate radiation shielding, the prominence and credibility of Muller as the dissertation mentor prompted broad acceptance of Ray-Chaudhuris findings in the scientific community. Indeed, the dissertation, flawed as it was, fortified the belief that Muller had induced gene mutations, and in so doing, thus discredited the threshold model. It is provocative, and troubling, to speculate that perhaps only Muller knew how – and to what extent - he had succeeded in manipulating the scientific community for his professional and ideological gain.

5. Science: the Stern-Uphoff one page note

The next important development for the generalized acceptance of the LNT model was the Manhattan Project studies of acute (Spencer and Stern, 1948) and chronic radiation-induced mutagenicity (Caspari and Stern, 1948). Both studies used the same *total* dose, but the acute study had a dose rate nearly 15,000-fold higher than the chronic study. As noted previously, these studies were the components of the total dose vs dose rate experiment proposed by Muller. In fact, the genetics research of the Manhattan Project under the direction of Curt Stern was simply a repeat of the Ray-Chaudhuri dissertation work (i.e., absent the translocation endpoint), but with considerably more resources and commitment. Muller wanted Stern to repeat Ray-Chaudhuris experiments because he must have recognized important limitations of the Ray-Chaudhuri study – about which he remained silent – and the new findings would be essential both for advancing his prior claim of inducing gene mutations and as support for the LNT.

Muller and Stern hoped that these experiments would yield the same amount of genetic damage whether radiation was administered all at once, or diffused over the lifespan of the fruit fly. That the acute study of Spencer was performed one year before the chronic study proved to be critical to eventual data interpretation, because important experimental features and research design strategies that were problematic in the Spencer study were avoided in the chronic study. For example, in the acute study, the temperature was poorly controlled, and the calibration of the X-ray equipment was variable and inconsistent throughout the study, and radiation was differently applied for the treatment groups. Further, data from multiple groups that received the same total dose, but with different dose rates, were combined, creating additional uncertainty in the analyses and interpretation of results. These and other study limitations that negatively affected study reliability (Calabrese, 2011, 2013) were, however, for the most part ignored by the radiation genetics community. Of particular note is that the chronic study (Caspari and Stern, 1948) did not have these methodological problems, and revealed no treatment effects, thereby supporting a threshold dose response rather than the LNT model (Calabrese, 2011).

The findings of the Caspari study (Caspari and Stern, 1948) caused considerable concern, with Stern initially rejecting the conclusions, incorrectly claiming that control mutation values reported by Caspari were aberrantly high. However, this assertion was disproved when Caspari provided adequate support from the literature (Calabrese, 2015). After retreating from this initial criticism (Calabrese, 2015, 2019a), Stern remained troubled and referred to the study in a letter to Edward Novitski as the “Caspari problem” (Stern, 1948 - letter to Novitski). After reading a draft of the Caspari paper, Milislav Demerec, the head of genetics at the Carnegie Institute, was also concerned, and asked what could be done to “save the hit model” (Caspari, 1947). Muller was also disturbed by the Caspari findings and tried to find ways to discredit the results; but, in his detailed letter assessing Caspari's results (Muller, 1947 - January 14), he admitted that “I have so little to suggest with regard to the manuscript.”

The Caspari study hence became the proverbial "fly in the ointment". It was a serious problem that plagued the viability and validity of the LNT model. Therefore, concerted efforts were made to discredit the Caspari study, and to promote the findings of the Spencer and Stern (1948) paper. In retrospect, it should be kept in mind that it was the Spencer and Stern (1948) study that displayed flaws, including some that were self-admitted, that were absent in Caspari's work (Calabrese, 2019a, 2020b).

Since the findings of Caspari were critical of an LNT interpretation, Muller convinced Stern to replicate the Caspari study. The experiments were attempted by Delta Uphoff, a new master's degree student at the University of Rochester, who worked with Stern. Uphoff undertook three experiments, each utilizing about 50% of the number of flies used in the Caspari study (ergo, each experiment had lower statistical power than Caspari's investigations), and there are other concerns with each of Uphoff's experiments (see Calabrese, 2011). The data from those experiments were neither peer reviewed nor published as full papers. A preliminary report of the first experiment was sent to the AEC, which was the funding agency, and was initially assigned "classified" status. A data-based manuscript presenting the other two experiments has not been identified, despite detailed efforts by one of the present authors (EJC) to obtain such information.

Uphoff's data were merely summarized in a one-page note in *Science,* where they were presented in a single table. The authors asserted that they planned to publish a detailed paper with appropriate research and statistical methods and presenting all relevant supportive data, but this never occurred. The paper describing the methods and results of that first experiment that was sent to the AEC offered an important disclaimer, stating that the data were "uninterpretable" due to aberrantly low control group values, and alluded to the possibility that this may have been due to investigator bias.[5] The fact that the investigators raised the question of possible bias is critical because the research climate, as established by Stern and Muller, strongly supported discrediting the threshold model while promoting LNT.

While it is not possible to satisfactorily resolve the bias issue post-facto, it is noteworthy that Stern was sensitive to this issue, and sought to block future criticism by acknowledging what was widely known: namely, that he and this team desired an outcome supportive of the LNT model. Such underlying bias makes it difficult both to detect and to clarify the influence it may have throughout the entirety of the research process from idea development, to the literature reviewed or ignored and to study design and operational features. It also is difficult to assess the extent to which bias could subjectively affect each member of the research team. Despite this, what is clear is that the Manhattan Project research under the guidance of Stern intentionally favored an LNT outcome and fortified its relative acceptance, value and durability within its research culture.

Given that Uphoff's third experiment also had a similarly low response control group value, it too should have been "uninterpretable". However, the questionable findings were published (in a highly summarized fashion) in *Science* again, without being peer reviewed. The publication became important to the radiation genetics community, and was the one that was principally cited to support LNT. In this way it had a demonstrably powerful effect both on the field and (radiation health) policy development.[6]

Despite attempts by Stern and his colleagues to discredit the Caspari study, its findings became even more problematic to Muller and Stern. Stern had hoped that he had "neutralized" the value of the paper, negating its scientific potency with a rather odd discussion section in the paper (Caspari and Stern, 1948) that at least implicitly (if not explicitly) tried to dismiss further use of the findings. But the prominent MIT radiation physicist Robley D. Evans (1949) saw through this language and used Caspari's data in a paper that he (i.e., Evans) published in *Science* that supported the threshold model. Because of Evans' prominence in the field, Muller became concerned, as revealed in a letter that he wrote to Stern on February 5, 1949 (Muller, 1949).

The issue became volatile after an Evans scientific presentation[7] became the subject of an editorial supporting the threshold concept, entitled "Radiation and Mutations" in the February 1949 issue of the magazine *Astounding Science Fiction* (unidentified Editor of magazine, 1949). While these comments attributed to Evans generated considerable interest, he also sent his Science publication to about 30 leading radiation scientists. Although Evans received positive responses from such leading radiation geneticists as Don Charles, James Neel, and even Curt Stern, Muller would not concede, writing to Evans in his typical argumentative style, which blended scientific points with inflammatory rhetoric (Creager, 2015).

The fact that Evans had made a considerable intellectual impression upon key members of the radiation genetics community may well have been why Muller chose to discredit the Caspari study. The challenge was apparently so serious to Muller that he acted without prudence, or ethical probity, and misrepresented the Caspari control group data while, at the same time, he contradictorily promoted the Uphoff findings that he had *previously* discredited in letters to Stern (Muller, 1950a, 1950b, 1954; Calabrese, 2013, 2015, 2019a). Yet, no one chose (or dared) to challenge Muller.

Through such imprudent actions, Muller blunted Evans' momentum and restored "order" by mitigating any intellectual challenge in the radiation genetics community. Based on available correspondence, it appears that Evans did not want a second round of Muller's tirades. The episode clearly showed Muller's intent to serve as the intellectual and (emotional) leader of the radiation genetics community.

6. BEAR I genetics panel - part 1: the Neel story

The nature and aptness of dose response models was debated in important non-government committees such as the NCRP, which Muller joined soon after being awarded the Nobel Prize. By this point, Muller explicitly advocated abandoning the threshold response in favor of the LNT model. On September 24, 1954, with Muller and Stern working together, the NCRP finally published a long-awaited report that supported the LNT, stating, "It has been shown experimentally that genetic changes can be produced with low doses of radiation. The frequency increases linearly with the dose in the case of gene mutations…. It may be taken for granted that the same effects occur in men." (National Committee for Radiation Protection (NCRP), 1954 - September 24, pp. 17, 19). Despite this adoption of the LNT model of radiation-induced genetic risks, immediate consequences did not follow. However, two years later Muller would again advocate the LNT model, when the US NAS BEAR I Genetics Panel was created. This situation was different, as recommendations by this panel would be highly visible, with a prominent publication in *Science* and front-page stories in the *New York Times*, the *Washington Post* and other leading venues, and with the final report being sent to all public libraries in the US (Calabrese, 2015, 2019a).

Obtaining the recommendation of the LNT model by the NAS BEAR I Genetics Panel should have been easy, but it wasn't. After all, the RF had been funding leading radiation geneticists for many years. The Director of Research for the RF, Warren Weaver, knew most key geneticists and their views on LNT. The entire BEAR I Panel of geneticists was comprised of committed supporters of the LNT model. The Panel even witnessed their LNT mantra, that all damage is cumulative, irreparable, and irreversible, being read into the official transcript without dispute (Calabrese, 2015).

Problems however arose on the first day of Panel meetings when James V. Neel offered the report of his recently completed 10-year study showing that there were no adverse genetic treatment effects in the children of atomic bomb survivors. Initially, the situation went just as Neel had hoped, with several Panel members, including Crow and Sonneborn,

[5] During the Uphoff experiments at the University of Rochester, Stern and Muller exchanged a series of letters in which Stern sought Muller's opinion of control group responses and whose data were the ones that had the most credibility, those of Caspari or Uphoff. The sequence of letters has been shared previously (Calabrese, 2013). Muller strongly supported the findings of Caspari. In fact, it was largely based on these exchanges that Uphoff and Stern (1947) deemed the experimental data of Uphoff and Stern (1947) as uninterpretable, citing Muller.

[6] It is important to note that Bentley Glass, a former Ph.D. student of Muller (and future member of the BEAR I Genetics Panel) joined the editorial board at *Science* in 1948, the year before the key non-peer-reviewed Uphoff and Stern (1949) paper was published. In a 1950 letter to Curt Stern, Glass indicated that he was the genetics section editor for *Science*.

[7] The Evans presentation was given at a symposium "On Certain Aspects of Atomic Warfare" on October 15, 1948 (Muller, 1949).

expressing the need to use human data in their assessments. But the ever-dominant Muller suppressed all such discussion by marginalizing the Neel study.[8] Muller's position was extreme because all data are valuable but limited, and data that appear to be "uninterpretable", like those non-peer reviewed findings (about mutations in the fruit fly) of Uphoff and Stern (1949), which Muller then endorsed, would therefore certainly appear to be limited in value.

Nonetheless, Muller prevailed, and the data from the 75,000 human subjects would not be discussed by the BEAR I Panel again. Still, Neel provided his report to a welcoming parallel British Genetics/Human Populaion Committee that acknowledged the value of his data, which had an influence upon the Committee's overall conclusions and recommendations. The British Panel stated: "We consider, therefore, that an individual could, without feeling undue concern about developing any of the delayed effects, accept a total dose of 200 r in his life-time, in addition to radiation from the natural background, provided that this dose is distributed over tens of years and that the maximum weekly exposure, averaged over any period of 13 weeks, does not exceed 0.3 r." (Medical Research Council (MRC), 1956). Evidently the British Genetics Panel agreed that there was indeed a threshold, in sharp contrast to the BEAR I Genetics Panel's recommendations to support and use the LNT model.

The findings of the Neel report repudiated the predictions of genetic damage in the first generation of US offspring that were made by the BEAR I Genetics Panel. The Neel report found no treatment-related effects over the ten-year period evaluated. Nevertheless, six experts of the Panel predicted from 2 to 10 million (best estimates) offspring being adversely affected by 10 rads in the first generation after exposure in the population of the US (which was ~160 million at that time). In the Neel study, exposures reached as high as 150 rads, with no demonstrated negative effect. The Panel had seen the Neel figures no later than the end of February (1956) when each member was provided with a copy of the summary chapter (Neel, 1956a - letter to Weaver, February 14; Neel, 1956b - letter/chapter to BEAR I Genetics Panelists, February 21). It is clear that the predictions for the first generation made by many of the BEAR I geneticists were strongly contradicted by the 10-year Neel study; and it must be presumed that they recognized this. Even so, they published their report in *Science,* with asserted predictions that were inconceivable in view of Neel's data, and without mention of the looming public conflict that could – and would – be generated by these human data. The BEAR I Genetics Panel chose to share its speculative estimates with the public, and there is no evidence of their feeling any responsibility to even mention the extensive ten-year study on the topic funded by the government on an actual human population that was exposed to the atomic blasts and which did not support the Panel's estimates, conclusions, and recommendations.[9]

This marginalization of the Neel study by the BEAR I Genetics Panel eventually led to a major public dispute between Muller and Neel, which created strong divisions among the radiation genetics community. When the Neel study was eventually released to the public during a major conference in Copenhagen in August 1956, it received considerable publicity (Calabrese, 2020a), which negatively affected the credibility of the BEAR Panel Report. This eventually forced the Panel to redirect its focus to cancer, and to engage the efforts of the young California Institute of Technology professor, Edward B. Lewis, under the direction of George Beadle, his department Chair. (See also, Section 10 of the present paper; and Calabrese, 2021a, 2021b).

7. BEAR I genetics panel - part 2: misrepresenting the research record

A second major event occurred during the early BEAR I Genetics Panel activities that further relates to, and contrasts with, the findings of the James Neel atomic bomb study. Because the Panel members strongly supported the LNT model, there was little to do once they affirmed their LNT mantra. In effect, their work was done. Because the budget permitted multiple meetings, Chairman Weaver asked the geneticists on the Panel to estimate the number of birth defect damage events in the US population that might occur with a given gonadal radiation exposure over the next one to ten generations (i.e.- as discussed above).[10] Three of the then 13 (later 12) geneticists declined to accept the challenge, believing that there was too much uncertainty to enable credible estimates. That left nine geneticists to accept the task. Although all were compelled to assume an LNT dose response model, their estimates, which were independently prepared over approximately 3–4 weeks' time, varied widely, and differed by many thousands-fold.

When panelist James Crow received the estimates, he was taken aback by the extent and degree of uncertainty and disagreement among the panelists.[11] He quickly realized the implications of this disagreement, and these were indeed concerning. If these nine distinguished geneticists were so uncertain and dissonant in their risk estimations, their recommendations would lack public credibility. Without providing unified and credible guidance, the Panel might just as well cease its activity. Apparently, on his own,[12] Crow chose to expunge the three lowest values, leaving just six estimates. This reduced the reported uncertainty by 80%, or down to about a difference between the extremes of 750-fold (mean value for the magnitude of the six ranges). This, in Crow's view, still suggested far too little concurrence. The Panel accordingly decided to state that there was only uncertainty of 100-fold (a nice round number often used in risk estimation), without further details or explanation provided. The 100-fold range of uncertainty employed by the BEAR I Genetics Panel was explicitly stated in the *Science* paper for the values of the six geneticists.

[8] In the November 20, 1955, transcripts of the BEAR I Genetics Panel, Crow stated (page 4) "We need to know more about man himself, about radiation." Sonneborn (page 5) then stated: "I agree with Crow that we need intensive effort to acquire information in regard to man. No amount of extrapolation is as relevant as the direct information on man himself". Neel (page 5) subsequently stated: "From the beginning of the ABCC [Atomic Bomb Casualty Commission] work until now this has been a major motive." Muller then killed the enthusiasm and fuller consideration of the Neel study with the following (page 6): "We should beware of reliance on illusory conclusions from human data, such as the Hiroshima-Nagasaki data, especially when they seem to be negative." After Muller's intimidating comments challenging the Neel study and its significance, Neel remained silent, allowing Muller's comments to stand. Muller's comments ended any further discussion of the major Neel ten-year study.

[9] In 1963 the BEAR Genetics Panel, in effect, repudiated their 1956 predictions of massive genetic damage/defects. They were then asked whether a second-generation genetic damage study should be undertaken of atomic bomb offspring (Crow, 1963). The panel subcommittee (Neel, Stern, Sturtevant) concluded the following: "It is highly improbable, in view of the results on the children of irradiated survivors of Hiroshima and Nagasaki, that studies of the grandchildren of these same persons could be expected to result in statistically significant evidence for the genetic effects of the atomic bombs." This statement unambiguously represents a striking repudiation of the Panel's earlier published transgenerational genetic damage predictions that supported its LNT position/recommendation. Despite this repudiation of their earlier report and rejection of the proposed study, this major conclusion was also hidden from the scientific community and general public, perhaps because it would have exposed them to serious questioning at the levels of both science and ethics.

[10] The memo of Weaver (February, 8, 1956) to the Panel stated that "….every geneticist on the panel was invited and indeed urged to undertake an estimation of the expressed damage due to detrimental mutations. The estimate was to apply to the total number of children (say 160 million?) which will in the future be born to persons now alive in the U.S.; and to their children and so on. At least three estimates are desired: 1) expressed damage to the first set of 160 million children due to a dose of 10 r to the persons now living; 2) expressed damage to the F_1 through F_{10} generations of children due to a single dose of 10 r to the persons now living; 3) expressed damage to F1 through F_{10} due to a dose of 10 r per "generation".

[11] Regarding the substantial uncertainty reflected in the Panel's estimates, Beadle, for example, was so uncertain that his genetic damage estimates ranged from a low of 100,000 to a high of 200,000,000. It was this type of uncertainly that Crow, Weaver and the other Panel members were afraid to share with the public. These estimates indicated that the so-called experts lacked insight into this problem and there was no consensus. And yet, even Beadle's low estimate was far too high based on the Neel human data.

[12] It remains unclear how Crow had the apparent audacity to remove the three most divergent estimates on the low end. One would have thought that he would have been strongly admonished and reprimanded because he was, in effect, altering the research record. He was actually falsifying the research record and thereby committing scientific misconduct. I (Calabese) have long wondered whether Crow may have received advice from Muller on the matter because they were close friends. A letter from Muller (1956b) to George Beadle, who replaced Weaver as chair of the panel, informs Beadle of the unresolvable conflicts he (i.e. Muller) had with the estimates of Demerec (bacterial-based estimates) and those from the human geneticists on the Panel. That Muller would only challenge the findings of these three individuals to Beadle, the only ones removed by Crow, leads to the above suggestion/possibility.

In essence, the statement further misrepresented data that had already been highly censored. For the six estimates (each presented as a range), the high and low estimates for each geneticist, or pair of geneticists, differed by 10-fold (Muller), 100-fold (Russell, Sturtevant), 288-fold (Crow), and 2000-fold (Beadle, Glass). The range of values was highly variable, even after removing the three (out of nine) most disparate values, and thus showed no evidence of consensus, which was a major concern for both Crow and Weaver. The 100-fold variation that the Panel provided in their *Science* paper did not conform to the mean (749-fold), the median (194-fold) or the geometric mean (221-fold). Since such a small number of estimates (i.e.- six) were provided, the Panel could have readily shared the entire listing as given above.

When the Panel published its paper in *Science,* it stated that 12 geneticists were invited to provide estimates of genetic damage, but only six engaged the assignment. However, the record indicates that this statement is not only incorrect, but is a deliberate deception because there were estimates provided by *nine* geneticists from differing fields and foci (with experimental experience ranging from work in bacteria to humans). Thus, it appears that the intention of Crow and the entire Panel was to mask the large inter-expert uncertainty in an attempt to encourage acceptance of the Panel's policy recommendations. In this way, the Panel falsified the record by dropping three estimates, and then reporting that only six geneticists accepted the invitation to provide the assessment (Calabrese, 2019a). Given this misrepresentation of fact in the journal *Science*, the Panel can be seen to have committed scientific misconduct. Furthermore, because Bentley Glass was a member of the Panel and also a senior editor at *Science*, his actions also implicate the highly respected journal as being complicit to the deception, as well. These duplicitous actions served to increase the likelihood that their recommendation of the LNT model would have maximal application and, thus, societal impact.

Additionally, the Panel refused to provide written scientific explanation for their decisions when asked to do so by members of the scientific community, thereby preventing elucidation and discovery of their actions. The President of the NAS was informed of the decision not to provide a report on the scientific foundation, and to let it stand as it was, in writing by the new chair of the BEAR I Genetics Panel, George Beadle (1957). This protected the decision of the Panel from further and more granular scrutiny.

8. Russell - part 1: the covered-up study

While the BEAR Genetics Panel was active, one of its members, William L. Russell, initiated a large study in 1956 to assess the potential of a single high dose (600 r) of X-radiation to induce dominant mutations that affected longevity or the incidence of cancer in the offspring of young adult male mice. When the offspring died, they were autopsied by G.E. Cosgrove, an experienced pathologist in the Biology Division of Oak Ridge National Laboratory (ORNL). When this study was completed in 1959, it was apparent that the massive dose of X-radiation had not influenced lifespan, as was also the case for the frequency, severity, or age distribution of neoplasms, including the range of leukemias, and other diseases. This represented a major finding that could have enlightened the debate on the reasonableness of the LNT model. Yet, it had no impact whatsoever at the time because Russell did not publish his findings until 34 years later (Cosgrove et al., 1993), and there is no evidence that he shared his findings with members of the BEAR Committee or any other advisory committees (or even with colleagues at ORNL). Even though Russell had completed that 600-R experiment with Cosgrove before the 1960 BEAR Genetics Panel Report was published, the experiment was not cited in that report. In fact, the wording near the front of that report provided a list of relevant information known at that time, which included: “There is some shortening of life in the progeny of irradiated male mice, as well as in the irradiated mice themselves.” Since Russell knew that the findings of his experiment with Cosgrove had failed to support his 1957 findings with neutron and gamma radiation (Russell, 1957) and did not demonstrate decreased lifespan, it is remarkable that he permitted that important statement to remain in the report unmodified.

The 600-R experiment was especially important in that it likely would have impacted scientific and policy debates regarding dose responses for mutations induced by radiation and other mutagens. By not revealing the findings, Russell protected the recommendations of the BEAR I Genetics Panel (1956). Perhaps a case can be made for Russell being intimidated by Muller if he had published negative data. Russell had seen firsthand how Muller professionally threatened the younger Neel following his prominent presentation of negative human findings of the atomic bomb study in 1956, and Russell may have sought to avoid such a confrontation with Muller (Calabrese, 2020a, 2020b). A 1989 reflective essay by Russell (1989) indicated how careful he had to be with Muller when publishing his 1958 dose rate paper, which suggested a possible threshold for mutation.

A striking, and most curious, development, in view of Russell's failure to disclose the results of his study with Cosgrove when it was completed in 1959, is that in 1991 Arthur Upton, a former Director of the United States (US) National Cancer Institute (NCI) (1976–1979), contacted Russell and told him that he had agreed to testify for the Defendants as an expert witness in an upcoming trial in the U.K (i.e. the Sellafield cases; see Wakeford and Tawn, 1994, for an extensive court case summary) in which the Plaintiffs claimed that irradiation of men working at the Sellafield facility had induced mutations that caused cancer in their children. (The significance of Upton contacting Russell is that Upton was pathologist Cosgrove's supervisor when that earlier (i.e., 1956–1959) autopsy study was done, at which time Upton was the director of the Biology Division Section dealing with somatic effects [e.g., cancer pathogenesis].) Upton thus obviously knew about the experiment conducted in 1956–1959 and realized that Russell's negative study was highly relevant to the Plaintiffs' claims of the high risk of cancer in the children of workers in a nuclear plant. Russell agreed to work with Upton in preparing a manuscript to help the Defendants. Russell called Cosgrove twice regarding their joint experiment (once late in 1991 and again in early 1992) and exchanged correspondence with him (Russell, 1992). Cosgrove was agreeable to publishing the experiment, but he told Russell that he could provide little assistance because of illness. Upton urged Russell to meet with the British Nuclear Fuels Ltd. (BNFL) legal defense and scientific team, which already knew about the study via Upton and had become extremely interested in having it published. The BNFL team held meetings with Russell and Paul B. Selby in the Biology Division of ORNL on March 10 and 11, 1992, during which Russell described his findings from the experiment completed in 1959 and agreed to prepare, with Upton and Cosgrove, the much-desired paper.

The details and implications of this story are published elsewhere (Calabrese and Selby, 2022). The 1956–1959 Russell-led study was indeed published in *Mutation Research* in 1993 (Cosgrove et al., 1993) and was influential in the U.K. litigation. That this three-decade-old study was of sufficient quality to pass peer-review in 1993 suggests that it may have been even more impressive in the time period around 1960 if Russell had sought to publish the findings then. Certainly, Russell and Upton appreciated the study’s findings and significance, even though they were willing to deliberately not publish that information. Statements that Russell made around the time of the trial indicate that he avoided publishing the study findings during the decades following its completion because he felt that the general public was not capable of fully understanding the results and of placing such findings into proper context.[13] To quote Russell directly, (as taken from the submitted version of the manuscript): It was, therefore, something of a surprise not to obtain a positive result in the experiment described here, and it was feared that publication of a negative finding could mislead the public into a false feeling of safety.[14]

[13] Russell's supervisor at the ORNL during this period was Dr. Alexander Hollaender. Russell and Hollaender were among the 13 original geneticists on the BEAR I Genetics Panel. It is not known whether Hollaender may have been involved in the decision to suppress the study findings.

[14] The exact wording from the submitted version of the manuscript is known because (see pp. 79–81 of the trial transcript of May 13, 1993) Mr. Spencer, a barrister for the Defendants, when taking the direct testimony of Selby, read, by accident, into the trial record most of the introduction of the submitted version of the manuscript before Justice French told him that the text being read did not agree with the version that he had. Selby then pointed out that some revisions had been made in the submitted version before the paper was accepted and that Justice French was reading from the version that was in press, from which Mr. Spencer then read.

Thus, Russell decided that he, and perhaps Upton, would suppress the findings of this government funded experiment. However, the publicity of the U.K. trial brought the study data into clear view of the public by challenging the assertions made by the Plaintiffs (viz.-that low dose radiation might induce heritable mutations capable of inducing large effects on cancer risk in first-generation offspring). Yet, this story is only now being shared with the scientific community. It has somehow been overlooked, or avoided, by regulatory agencies (Calabrese and Selby, 2022), even though this trial was a major news story for many months in the U.K. In fact, when Upton chaired BEIR V (1990), he apparently never shared the study findings with that committee. Likewise, Upton failed to share this information during the OSHA cancer policy hearings in 1978 at which he provided repeated testimony as the Director of the US NCI.

9. Russell - part 2: the dose rate story and LNT public policy based on mistakes

The next major focus on the validity and value (or lack thereof) of the LNT model was engaged by the BEIR I Genetics Committee, formed in 1970, and which eventually provided key guidance to the EPA to use the LNT model for cancer risk assessment. Russell's dose rate data would again be at the center of debate (Calabrese, 2017a, 2017b). In 1958, Russell et al. (1958) showed that radiation-induced genetic damage was capable of being repaired in spermatogonia and oocytes. These findings were significant because they directly contradicted assumptions and conclusions of the BEAR I Genetics Panel (National Academy of Sciences (NAS)/National Research Council (NRC), 1956), and its reliance on and use of LNT dose response regulatory risk assessment principles. In Russell's studies, oocytes did not show mutational damage until dose rates of radiation exposures approached 30,000-fold greater than background (Russell, 1969). Stem-cell spermatogonia also showed consistent capacity for repair of genetic damage, although at lower efficiency than in oocytes. In these investigations, a threshold for spermatogonia was not achieved. The reason for the lack of a threshold remains unclear, but could have been due to the experimental protocols, which limited exposure options, or by the choice of the 7 genes tested in the specific-locus test. The claim that there was no threshold in spermatogonia became somewhat established as fact, with no effort being made to pursue the critical issue of effects from substantially lower dose rates.

During the BEIR I Genetics Subcommittee (National Academy of Sciences (NAS)/National Research Council (NRC), 1972) meetings, the prior mistake of presuming this absence of reparatory capacity which was originally made by the BEAR I Genetics Panel (National Academy of Sciences (NAS)/National Research Council (NRC), 1956) was acknowledged. However, the recommendations regarding the use of the LNT model were re-affirmed in light of the espoused and widely held belief that there was no threshold in stem-cell spermatogonia.

It is now known that the BEIR I (National Academy of Sciences (NAS)/National Research Council (NRC), 1972) LNT recommendations were especially problematic from the start. This was because committee member William Russell failed to disclose the lack of support for his early (rather sensational) conclusion that ionizing radiation induces many dominant mutations that decrease longevity in mice. It was also because Russell's first experiment (Russell, 1951), which demonstrated the induction by X-radiation of recessive specific-locus mutations in male mice, was severely compromised by (undisclosed) complications with the control mutation frequency. It is rather astounding that it took 45 years after this complication first occurred before the Russells acknowledged (Russell and Russell, 1996) a problem caused by their failure to report, in experiments on radiation-treated males and their controls, the occurrence of clusters of specific-locus mutations that arose in experiments in the offspring of parents that they called “masked mosaics”. Thus, the problem was first acknowledged 24 years after the BEIR I report was published.

That long delay in reporting ceased when one of the authors of the present paper (PBS), a team member of the Russell program at ORNL for over two decades ending in 1995, and the only Ph.D. student that William Russell ever had, discovered a pervasive cluster error that affected the massive database for specific-locus mutations and reported it to the Department of Energy (DOE). Details relating to how this error was detected and some of the developments that followed have been published elsewhere (Selby, 2020). The DOE insisted upon an investigation in which an Ethics Investigation Committee of four outside scientists was established to evaluate submitted materials and meet with the individuals involved from July 21–24, 1996. The Russells were instructed to publish their data on clusters, and (against the advice of Selby) were permitted to perform the reevaluation in its entirety by themselves, presumably with the help of their research staff. Their effort culminated in two papers that were published in *Proceedings of the National Academy of Sciences (PNAS) USA* (Russell and Russell, 1996, Russell and Russell, 1997).

The Russells admitted that rarely their specific-locus experiments contained unreported clusters of specific-locus mutants among the offspring of what they called “masked mosaic” parents (Russell and Russell, 1996, 1997). Selby (1998a, 1998b) refers to such clusters as First Cleavage Gonadal Mosaic clusters (FCGM clusters) in order to clarify that they are clusters produced according to the hypothesis advanced by Liane Russell (1964) in a paper that provided no indication that the clusters in question were found among offspring in specific-locus experiments. In their main publication (Russell, 1964, Russell and Russell, 1996), the Russells agreed that there were six FCGM clusters found among the offspring of 37,735 fathers used in their radiation experiments (including males from radiation treatments with their unirradiated controls, as well as untreated controls in experiments on chemicals). Therein they agreed that Selby was correct that there had been under-reporting of the per generation spontaneous mutation rate in mice; and they stated that the correct value, based upon their analysis of their vast experimental data, was a 2.2-fold multiple of the data that they had previously reported. Selby’s estimate of the error for this particular comparison, based on computer simulation of specific-locus experiments, was about a 3-fold error. After Selby initially reported the problem to the DOE, and especially in view of additional information obtained during the next few years, he later increased his estimate (Selby, 2020) to there being at least a 10-fold error (Selby, 2020).

Some 20 years after the Russells claimed that their error was only 2.2-fold (i.e., in 1996), Calabrese (2017a, 2017b) applied the Russells' correction to the status of the data at the time of the seminal 1972 BEIR I LNT recommendation. He concluded that if the Russells' correction had been known so that it could have been applied by BEIR I (National Academy of Sciences (NAS)/National Research Council (NRC), 1972), a threshold for males and a hormetic dose response for females would have been demonstrated, perhaps thereby changing the history and subsequent course of cancer risk assessment. Now that we (EJC and PBS) have learned much from each other, some of these issues will be more closely reexamined and discussed in more detail in future publications. It is apparent that there have been significant mistakes that BEIR VII and the EPA should have been aware of for some time, but, as yet, there is no evidence that these mistakes have been addressed and/or corrected.

10. Science: publishing the Lewis paper

A major extension of the BEIR I (National Academy of Sciences (NAS)/National Research Council (NRC), 1972) LNT recommendation to include LNT as the model for cancer risk assessment was strongly influenced by the 1957 Lewis paper on leukemia. The EPA accepted the LNT model recommendation by BEIR I and applied it to ionizing radiation and chemical carcinogenesis (Albert, 1994). A detailed reassessment of that influential Lewis (1957) paper reveals it to be scientifically flawed and biased. To make matters worse, Lewis' work was published in *Science* along with a powerful editorial endorsement, which was quite rare, and which made this paper especially noteworthy. This promotional effect likely resulted in Lewis becoming part of a feature story on radiation risk in *Life* magazine, and his testifying to the US Congress, both within one month of publication of the *Science* paper.

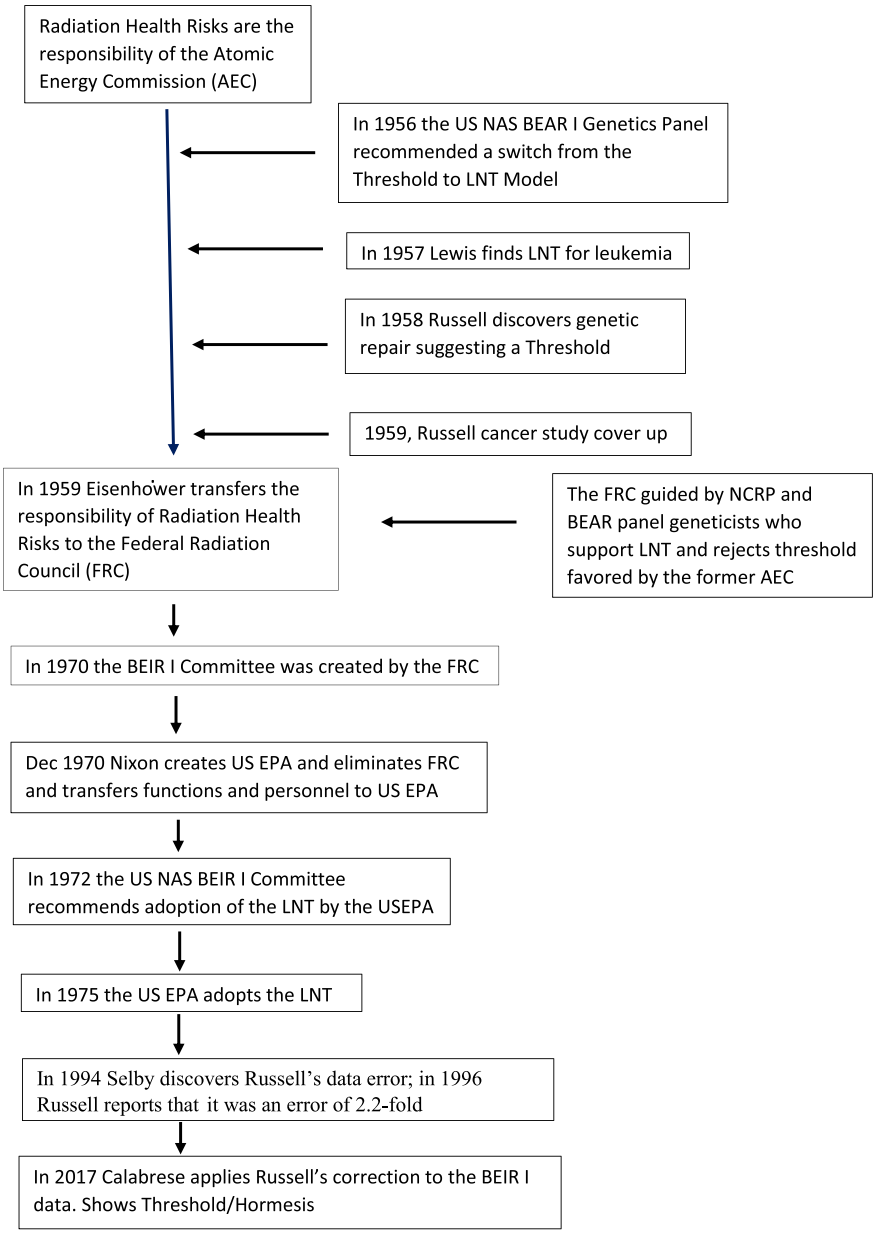

Fig. 1. LNT organizational flow chart.

Despite its powerful impact on the adoption of the LNT model for cancer risk assessment, concerns have been raised about (1) Lewis' qualification (s) to undertake this study (i.e., as based on his lack of scientific education and training in epidemiology, cancer biology, radiation chemistry and dosimetry, and quantitative risk assessment methods), as well as (2) the scientific quality and objectivity of the paper (Calabrese, 2021a, 2021b). For example, Lewis focused on the occurrence of leukemia in four groups exposed to ionizing radiation: (1) the victims of the atomic bomb (AB) explosions; (2) patients with ankylosing spondylitis (AS); (3) patients with enlarged thymus (ET); (4) and radiologists. In each case, Lewis did not perform appropriate due diligence regarding and/or intentionally miscommunicated the status of the science. Notably, in the case of AS, the authors of the key study and its high-level scientific oversight committee independently stated that the study could *not* be used for low dose cancer risk extrapolation; however, Lewis did so without presenting these important opposing views (Court-Brown and Doll, 1957). In the case of ET, the authors of the critical study specifically stated that there was *no* causal relationship between the radiation exposure and leukemia in their patients, a view that Lewis again failed to represent (Simpson et al., 1955, Simpson and Hempelmann, 1957). The radiologists' data used by Lewis included massive radiation exposures in earlier decades, thus making low dose risk predictions of little value. These facts also were not reported or discussed in the Lewis paper. Lewis's interpretation was soon thereafter discredited in a follow-up study employing more relevant levels of occupational exposures (Court-Brown and Doll, 1958). With respect to the AB patients, the Lewis analysis misrepresented the dose response in the low dose range by combining exposure groups, which led to a distorted dose response from which linearity was concluded. Numerous other analyses of the AB patient data with non-combined dose spacing reveal either threshold or J-shaped dose responses, which also were not addressed by Lewis (Calabrese, 2021a). Lewis made no attempt to consider alternative possible causation, nor did he discuss the other possible causal explanations that had been offered by other researchers at that time.[15] The apparent failure to scientifically vet the Lewis paper calls into question the nature, integrity, and perceived probity of peer review at *Science* at that time.

[15] Bentley Glass was one of only six senior editors of *Science* at this time and also was a member of the BEAR I Genetics Panel.

11. Discussion

The historical foundations of the LNT model were established with Muller's (1927a) paper proclaiming his elicitation of gene mutations by X-rays, and his subsequent proposal for a Proportionality Rule in 1930, which continues to be applied to the present (Fig. 1, see time flow chart). The LNT history is shown here to be punctuated – if not defined - by a combination of previously unknown and/or ignored mistakes, apparent deceptions, and unsupportive assumptions, within historical, contemporary, and arguably ongoing legacy, which the scientific and regulatory communities have thus far shown little interest in clarifying or rectifying. Yet, these rather unstable (and we opine scientifically unsound and unethical) foundations have served as the basis for pervasive cancer risk assessment principles and practices.

Among the common themes that emerge in the present assessment is the long and pervasive influence of Muller upon other radiation geneticists, and their collective efforts to persuade the scientific community to adopt the LNT model when estimating radiation-induced hereditary damage and cancer risks. It took Muller and his colleagues nearly 30 years to achieve this transformative influence, as evidenced by the iterative recommendations of the NCRP, NAS, ICRP, FRC and other groups. Indeed, history portrays radiation geneticists, as a group, to be well-organized to ensure influence upon major advisory bodies.

The present paper provides several new and unique historical perspectives. It is the first to suggest that the most significant impact of the BEAR I Genetics Panel was its erosion of the credibility of the AEC within the political domain. This erosion of confidence resulted in Eisenhower transferring health risk assessment from the AEC to a new federal organization (FRC). The FRC then adopted the LNT model, based upon the diligent efforts of LNT ideologues who served as advisors to committees and organizations that established the basis and framework. These actions enabled the LNT model to be insulated from scientific criticism within an expanding environmental bureaucracy. This paper elucidates that one of these advisors, William Russell, suppressed major findings of a radiation cancer study that could have significantly challenged acceptance of the LNT model (Cosgrove et al., 1993; Calabrese and Selby, 2022).

When regarded in this context, it is apparent that the LNT model was evaluated and adopted by regulatory agencies in ways that transgressed ethical standards – both of the time, and certainly at present. The FRC was advised on matters of radiation risk assessment by Russell while he was failing to report a major complication throughout his decades of specific locus test (SLT) experiments related to the origin of spontaneous mutations, which might have caused errors (which could be large if the actual data were known) in his estimates of control and experimental mutation frequencies and their applications to radiation risk estimates in humans. Such scientific misconduct is indefensible, both as focal to the sound practices of research, and with regard to violating the public trust – and public good – of science as a humanitarian enterprise.

The processes of accepting and advocating the LNT model were also markedly affected by the unprofessional actions of the journal *Science*. For example, the Muller paper of 1927 lacked data, yet was published, and created a major transformation in the research community. Muller's (1928) data-based paper was never peer-reviewed. It took quite some time, but it was eventually shown that Muller did *not* induce gene mutations, but instead primarily evoked very large gene deletions in chromosomes. Yet, it was upon these misunderstood realities that the LNT single-hit model was formulated. As well, the 1949 Uphoff and Stern (1949) note in *Science* that criticized the threshold findings of Caspari and promoted LNT was not peer-reviewed; and data from two of the three Uphoff and Stern experiments have been missing for 70 years.

The radiation genetics community, NAS BEAR I Genetics Panel, and EPA have never acknowledged these issues, instead only citing the non-peer-reviewed (one-page) note by Uphoff and Stern (1949), some of which was deemed as "uninterpretable" by the investigators themselves (Uphoff and Stern, 1947). The journal *Science* also published the BEAR I Genetics Panel LNT recommendation, which is now known to be the product of falsification of the research record, and on which one of their senior editors (i.e., Bentley Glass) served as a co-author (National Academy of Sciences (NAS)/National Research Council (NRC), 1956). *Science* also published the highly influential but profoundly biased paper of Lewis (1957) which address and advocated the use of the LNT model in cancer risk assessment, and afforded the paper a strong accompanying editorial endorsement. These actions were reflected in the flamboyant performance of Muller at his Nobel Prize Lecture in which he announced the demise of the threshold model based on the Ray-Chaudhuri dissertation (that has now been discredited). We opine that retrospective insight into Muller's awareness of such subterfuge, brazen promotion of flawed research, explicit bias, and professional bullying can only be seen as unethical. Further, the intentionality of his acts were wholly malfeasant, if not frankly immoral.

The thematic features comprising the historical foundations of LNT and cancer risk assessment are substantial and well-documented, and were significant drivers that ensured the adoption of the LNT model by both the regulatory community and society at-large. In this light, we believe that the policy-based framework of cancer risk assessment that affects all developed countries is *not* based upon "best available science", but rather is founded on unbridled historical professional cupidity, personal egoism, and manifest intimidation. The scientific community allowed (and in many ways, enabled) this to happen, ignored both the core precepts of the philosophy - and lessons from the history - of science, and irresponsibly disavowed public trust. Yet, many of those who engaged and committed these unethical practices and deeds were the recipients of prestigious awards, generous funding, and eponymous institutes and lectures.

It is unwise to show the past in the light of the present, and that is not our aim. Rather, it is to illustrate that the ethical precepts fundamental to maintaining science as a public good-in-trust were well-known, recognized, and acknowledged when and as these events occurred. Thus, these acts were as inapt and impugnable then as they are today, and their effect was not restricted to their time, but instead, negatively affected the lives of countless individuals (then and to this day) who placed their trust, health, and existential vulnerability in the assertions and guidance of recognized experts.

The challenge, task, and opportunity is what to do about such actions today. An invaluable first step is to inform the scientific and policy communities about this underlying history. The well-worn adage is that those who fail to heed history are doomed to repeat it. The stakes are far too high to allow that to happen. To prevent this, we posit that integrative scientific and ethico-legal education and training should serve both as a lens to peer deeply into the history, nature and occurrences of such problems, and as a mirror to reflect upon our current practices, institutions and policies (e.g., LNT) with the same intensity and detail. We hope that this will prevent similar occurrences presently, and lead to the correction of damage to society resulting from ideologically driven science policy of the past, and in the future.

Credit authorship contribution statement

EJC conceptualization, writing original draft; PBS and JG reviewed, revised, and edited the manuscript.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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