Arch Toxicol
DOI 10.1007/s00204-013-1105-6

REVIEW ARTICLE

How the US National Academy of Sciences misled the world community on cancer risk assessment: new findings challenge historical foundations of the linear dose response

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Received: 24 April 2013 / Accepted: 11 July 2013

Abstract This paper extends several recent publications indicating that Hermann J. Muller: (1) Made deceptive statements during his Noble Prize Lecture on December 12, 1946, that were intended to promote the acceptance of the linear dose-response model for risk assessment for ionizing radiation and (2) that such actions of Muller were masked by a series of decisions by Muller's long-time colleague and esteemed radiation geneticist Curt Stern, affecting key publications in the mutation literature. Such actions further enhanced acceptance of the linearity dose-response model while preventing Muller's deceptions from being discovered. This paper provides documentation that Muller reinforced such practices within the scientific literature in the early 1950s, by supporting scientifically questionable actions of Stern. Detailed documentation is provided that demonstrates how these actions affected national and international risk assessment policy for ionizing radiation and chemical carcinogens via the recommendations of the National Academy of Sciences Biological Effects of Atomic Radiation committee in 1956, to adopt the linear dose-response model.

Keywords Mutation · Linearity · Dose response · Risk assessment · History of science · Muller

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Introduction

It was recently discovered that the 1946 Nobel Prize Lecture for Biology and Medicine by Laureate Hermann J. Muller misled the audience on the nature of the dose response in the low-dose zone concerning the effects of ionizing radiation on germ-cell mutagenicity to advance an ideologically motivated risk assessment policy (Calabrese 2011a, b, 2012). Evidence to support this conclusion is found in Muller's own words from letters he sent to Professor Curt Stern of the University of Rochester, an expert in radiation genetics. Stern sent Muller a manuscript by Ernst Caspari and himself on November 6, 1946, for review as Muller was a paid consultant to the project (Calabrese 2011c). This manuscript demonstrated support for a threshold dose response, while challenging the linear dose-response single-hit mutagenicity mechanism model, based on an extensive study of ionizing radiation on mutation in the germ cells of male fruit flies. On November 12, 1946, Muller acknowledged receipt, noting that the findings strongly challenged the linearity dose-response concept and, given their importance, needed to be replicated as soon as possible (Calabrese 2011c). This long-term study used the lowest ionizing radiation dose rate yet reported. Despite this new information, Muller would go on to deliver his Nobel Prize Lecture some 5 weeks later (December 12, 1946), proclaiming that one could no longer consider the possibility of a threshold dose response for germ-cell mutagenicity. The only option, he argued, was to switch to a linearity dose-response model for risk assessment (Muller 1946a).

Muller, of course, made these public claims while knowing that the most extensive and relevant testing supported a threshold interpretation. A letter from Muller to Stern 5 weeks after the Nobel Prize Lecture (January 14, 1947)

Published online: 04 August 2013

confirmed his support for study replication, that he had no technical criticisms of the Caspari study, and supported publication especially in view of the caveats worked into the discussion, hopefully preventing acceptance of a threshold interpretation (Calabrese 2012; Lilly Library 1947a, January 14 letter). In effect, Muller told the Nobel Prize Lecture audience one story while in private correspondence he revealed a profoundly different view. According to his former student, friend, and colleague, Crow (1995), it was well known that Muller would try to win arguments by exaggeration and overstatement. Crow found this behavior exasperating as Muller would often end up hurting his case by unnecessarily misrepresenting facts and circumstances, incorrectly thinking it would help him win his argument. This same behavioral trait was evident at the Nobel Prize Lecture.

Before his Nobel Prize Lecture, Muller sought to raise concern over the public health implications of ionizing radiation and to change the risk assessment process for ionizing radiation from the use of a threshold dose-response model to the far more conservative linear dose response. This goal was essentially shared by the entire radiation geneticist community. Following his Lecture, Muller would now have two goals: Protecting his reputation by ensuring that his misleading comments would not be discovered while still aggressively pushing acceptance of the linearity agenda. Both goals were entangled; being such an important scientist and leader any fall in Muller's status would have a devastating impact on the acceptance of the linearity dose response, especially if it involved an ideological misrepresentation about the linearity concept. Muller achieved both goals due to decisions of Stern that discredited the findings of his colleague and co-author Ernst Caspari, thus saving Muller from criticisms about his Nobel Prize Lecture while supporting the questionable findings of Delta Uphoff, another co-author. Muller's misleading comments and the Stern's apparent data obfuscations would not be revealed for more than 60 years while the linearity acceptance goal by regulatory agencies worldwide was attained. The present paper extends the recent reports of Calabrese (2011a, b, 2012) with newly discovered findings that demonstrate a carefully focused and timed set of inexplicable scientific judgments by Muller concerning the nature of the dose response. These actions reinforced his Nobel Prize Lecture comments and the actions of Stern that enhanced the goal of achieving a switch from threshold to linearity. This paper also demonstrates the profound impact of the Stern/Muller actions on the radiation genetics community based on the scientific publication record and dose–response recommendations/conclusions supporting a linearity dose–response risk assessment model by the highly influential NAS BEAR I Committee, Genetics Panel.

Part 1—Stern's plan to promote linearity

Curt Stern was a long-time supporter of the idea that ionizing radiation affected germ-cell mutation in a linear dose-response manner. He expected that this would be observed in studies he was directing under the aegis of the Manhattan Project using fruit flies. While a linearity dose-response was reported in acute studies with X-rays (Spencer and Stern 1948), the most significant test would take place with the research of Ernst Caspari when gamma radiation would be administered up to a 13,200-fold lower rate than in the Spencer research. In a troubling development, Caspari reported to Stern that his findings did not support a linear interpretation but rather a threshold dose response. Based on letter correspondence between Stern and Caspari, Stern initially refused to accept this interpretation, arguing that the mutation threshold response was most likely due to unusually high control group values (i.e., spontaneous mutations in sperm stored in the spermatheca of the female for 3 weeks) which masked a radiation-induced treatment effect (Calabrese 2011b). Caspari then researched this issue by exploring the literature and obtaining substantial unpublished data on this specific issue from Muller based on research during his appointment at Amherst College (1940–1945). Caspari argued that his control group mutation data were not aberrant but consistent with the literature and Muller's data for aged sperm whether stored in the spermatheca of the female or in the male. As a result of the Caspari analysis, Stern withdrew his objection and accepted the conclusion that the control group spontaneous mutation values were within the normal range. Since Stern could not dismiss the findings of Caspari due to the controls, he then opted for an alternative but bizarre strategy to marginalize the threshold dose-response conclusion. Stern directed the manuscript discussion to explain why these data should not be accepted and utilized until it was determined why Caspari's findings differed from those of Spencer and Stern's acute study which they claimed supported linearity. It was this manuscript of Caspari that was sent to Muller for review just prior to his Noble Prize Lecture.

It is odd that investigators reporting on striking new findings, using the most advanced methods and the lowest dose rate yet studied, would demand the reader not take the data seriously. Stern placed no such restriction upon the Spencer paper, a study with considerable methodological limitations [e.g., inadequate control groups, inappropriate data combining for statistical analysis, lack of adequate X-ray instrumentation calibration, poor temperature control, and dose rates differing by as much as 10-fold (10 and 100 r/min) between treatments, thereby creating two experimental variables within one experiment] (Calabrese 2011b). Furthermore, there were at least two dozen significant methodological differences between the two studies

making them not directly comparable. Stern published the manuscript (Caspari and Stern 1948) with its misdirected discussion, without apparent independent, peer review in the journal for which he was the editor, that is, *Genetics*.

Comment

Based on this temporal sequence, it would appear that the principal driving force to challenge the Caspari findings that supported a threshold interpretation was his advisor and co-author, Curt Stern. It was Muller who indicated that the findings of Caspari needed to be replicated since they were contrary to a linear single-hit dose-response interpretation. Of particular note, however, was that the only changes made to the Caspari manuscript following the review of Muller was to add the name of Muller to the acknowledgments section and to remove the statement from the conclusion that the findings supported a tolerance or threshold interpretation (Calabrese 2011b).

Part 2—the replication studies

Since Ernst Caspari and Warren Spencer were no longer available to continue experimentation, Stern engaged the services of a Master's student, Delta Uphoff, to assess why the Caspari study did not support a linear interpretation. The results of the initial experiment were deemed by Stern as not usable as her control group spontaneous mutation rate was strikingly low, being outside the expected range for aged sperm (~40 % lower than expected); no conclusions could be drawn from the study (Uphoff and Stern 1947). A similar very low control group spontaneous mutation rate response for aged sperm in her second experiment would also make such data uninterruptable. In her third and final experiment, Uphoff reported control values in the normal range for aged sperm but the radiation treatment response was itself aberrant, far exceeding predicted responses assuming low-dose linearity (Calabrese 2011b).

Stern: What to do next

Finding a way to support linearity was the prevailing theme. For example, when Caspari had shared his data with the Head of Genetics at the Brookhaven National Laboratory and future member of the BEAR I Committee/Genetics Panel, Milislav Demerec, he wrote to Caspari asking what can be done to save the single "hit" linearity dose-response paradigm (Calabrese 2011b; American Philosophical Society 1947f, September 25). The "hit theory" for ionizing radiation-induced mutation was first postulated by Timoféeff-Ressovsky et al. (1935), providing a theoretical mechanistic foundation for the LNT dose-response model. Given his goals and ideology, Stern had little choice. Another experiment was not going to be practical as Uphoff would leave for a position with the NIH. In the absence of new data, Stern decided upon a new strategy to "save" the single-hit linearity dose response. In order to achieve this goal, he would have to do two things: (1) Reverse his position on the Uphoff control group data, declare that they are normal, not aberrant, making the Uphoff experiments now interpretable and (2) challenge further the credibility and acceptance of the Caspari study (i.e., beyond the misdirected discussion of the Caspari/Stern paper). Stern took the bold action of asserting that the Uphoff control group data were part of the normal distribution. He offered no explanation or assessment of the literature to justify this conclusion. This would not be difficult as only very few people would have known about his earlier concerns with the Uphoff control group data, since the manuscript (Uphoff and Stern 1947) detailing such concerns was never submitted for publication but was placed in the Atomic Energy Commission (AEC) archives, initially as a classified manuscript. Thus, the written critique of the Uphoff control group data and letter communications on this topic were generally not known or available.

The Uphoff and Stern (1949) paper also raised a number of doubts about the Caspari paper such as whether its non-treatment effect/threshold finding was the result of "errors in sampling." Given standard professional protocol, the "errors in sampling" hypothesis was a surprising and unexpectedly harsh challenge to the work of Caspari, a University of Rochester team member, especially since this criticism had never been raised previously by Stern, Muller, or others in previous detailed evaluations. In fact, there was never any documentation to support this possibility. Further, Stern also raised the specter of the Caspari control being elevated by unnecessarily stating that his control group was higher than each of the controls of the three Uphoff experiments. Stern neglected to state that two of the Uphoff studies had aberrantly low control group values based on the published literature and Muller's data. This decision by Stern would now make the Uphoff experimental data "interpretable," whereas several months before he judged it as "uninterpretable." Also, the third Uphoff experimental control data were indistinguishable statistically from the Caspari control (0.2489 vs. 0.2352 %). Such actions helped to achieve the above-stated goals of enhancing the credibility of the Uphoff data while marginalizing the Caspari findings.

The Uphoff and Stern (1949) paper changed the way the Caspari data (Caspari and Stern 1948) were perceived and accepted by members of the scientific community. Below are quotes from several papers (Higgins 1951; Singleton 1954a, b) and a dissertation (Jolly 2004) that address very

clearly how the Uphoff and Stern (1949) paper marginalized the research of Caspari. Of particular significance is that the judgments drawn by each of these papers were factually and interpretationally incorrect.

Higgins (1951) stated that "Uphoff and Stern (1949)…concluded that low-level radiation does produce mutations in fruit-fly sperm and that the apparent inconsistencies of previous results were due to different experimental techniques and errors in sampling" (page 10, column 1).

Singleton (1954a) stated that "Caspari and Stern (1948) studying chronic gamma radiation found no increase over controls for doses of 2.5 r/day for 21 days. However, it was later documented by Uphoff and Stern (1949) that the controls used by Caspari and Stern had an abnormally high sex linked lethal frequency and that actually there was an effect of the chronic gamma radiation of 2.5 r/day." (page 599)

Jolly (2004) stated (1) that "Stern and Caspari initially detected no significant difference in the mutation rates on the controls and the irradiated flies, though later they corrected for experimental errors and got a statistically significant difference." (pages 78–79) (2) "The results of Stern's initial experiment failed to support the linear hypothesis for genetic injury. Assuming that something must have been wrong with the experiment, he eventually identified experimental errors, which, when corrected for, supported linearity." (pages 80–81).

Caspari's control group data were therefore once again challenged by Stern; the once aberrantly low controls of Uphoff were now seen as being in the normal range. With these changes, the dose response of the collective grouping of the Stern Drosophila experiments would appear linear. This is the conclusion of what Uphoff and Stern published in their one-page technical note in the 1949 *Science* article summarizing the Spencer and Stern (1948) and Caspari and Stern (1948) papers and the three Uphoff experiments. This 1949 paper, as noted above, did not include mention that the previous conclusions (Uphoff and Stern 1947) about the Caspari and the Uphoff control groups that had been reversed by Stern and the role of the Muller data assessment in the decision-making process. Since the Uphoff and Stern (1949) brief technical paper lacked any information on research methods and other relevant data, the authors promised a detailed follow-up publication to correct this critical limitation, a promise never fulfilled. Given the lack of information provided in the *Science* paper and the prestige of this journal, it raises a question about the circumstances surrounding its publication within this context. It should be noted that Hermann J. Muller's first graduate student (i.e., H. Bentley Glass) became an editor at *Science* in 1948, only months prior to the submission of the Uphoff and Stern manuscript. Glass also had a relationship with Stern with whom he had been awarded a National Research Council post-doctoral fellowship at the Kaiser Wilhelm Institute in Berlin (Erk 2009). Since Glass was an expert on *Drosophila* radiation genetics, it is likely that he oversaw the evaluation of the manuscript. One must also question to what extent Muller/Stern may have exploited their relationship with Glass to facilitate the publication of such a limited paper and used the journal to advance an ideological perspective.

Muller's post Nobel Prize dose–response comments about the Caspari and Stern (1948) study

Muller's statement

In his 1950 article entitled "Some present problems in the genetic effects of radiation" in the *Journal of Cellular and Comparative Physiology* Muller (1950a) provided an explicit characterization of the Caspari and Stern (1948) findings. Muller stated on page 10 "A recent paper by Spencer and Stern…….extends the principle (i.e., one-hit principle) down to total doses of 50 r and 25 r." In the next paragraph, he stated: "It is true, in a parallel paper… .Caspari and Stern have reported results somewhat deviating from the above."

Comment

Muller trivialized the significant challenge of the Caspari study to the linearity dose-response paradigm. The key Muller phase concerning the Caspari data is "somewhat deviating". The Spencer and Stern (1948) study involved an acute exposure, that is, all doses of radiation were administered within a few minutes to a few hours. In contrast, the Caspari and Stern (1948) study provided the same total dose as in the Spencer and Stern study but spread over 21 days, at a dose rate up to 13,200-fold lower. The "somewhat deviating" results were such that at the lower dose rate of the Caspari and Stern study, the data supported a threshold interpretation, not the expected linear proportionality response. Muller was quite concerned with the Caspari study as it represented a potentially significant challenge to linearity, repeating this perspective in letters (Lilly Library 1947a, January 14; American Philosophical Society 1946, November 12) to Stern and emphasizing the need to replicate this study, despite the requirement for additional funding and the efforts of multiple scientists and staff for about 1 year. It is also important to note that Muller never mentioned any of the numerous methodological/analysis limitations/flaws of the Spencer and Stern (1948) in any of his publications.

Muller's statement

In footnote 1 on page 10 of the above-cited article, Muller (1950a) stated that "Uphoff and Stern have published a report of further work, with doses as low as 50 r, given an intensity as low as 0.0165 r per minute. The results obtained are entirely in conformity with the one-hit principle. A consideration of these results, together with the early work, leads to the conclusion that the deviation first referred to (the Caspari and Stern 1948 findings) was caused by a value for spontaneous mutation rate that happened to be unusually high."

Comments

Muller claims that the research of Delta Uphoff and Curt Stern is "entirely in conformity with the one-hit principle" (Timoféeff-Ressovsky et al. 1935). What Muller neglected to state was: (1) Uphoff's first experiment displayed an aberrantly low control group response based on Muller's own extensive data involving some 200,000 fruit flies (Muller 1946b). A letter from Curt Stern to Ernst Caspari (undated) (American Philosophical Society Undated, circa July-Aug 1947) addressed the control group issue. It states: "The radiation data continues to be puzzling. Delta's difference between control and exper[imental group] appears to be due mainly to a much lower control group value than yours. However, Muller informs me that his data give an aged control value close to yours. Thus, my first idea that your results could be "explained away" by assuming that your control value happened to be unusually high, seems unlikely. Rather does Delta's control appear too low. Well, we'll have to meet." Muller provided this information to Stern twice in letters dated February 3, 1947, and August 4, 1947 (Lilly Library 1947b, c). It should be noted that the occurrence of increased mutations in aged sperm in the control group as reported by Caspari was not a new concept to Stern. In fact, when Timoféeff-Ressovsky first presented such data in the late 1930s, Stern corresponded with Demerec specifically addressing these findings. These letter exchanges reveal not only Stern's knowledge of the findings, but also of his knowledge that the findings had been subsequently replicated (Lilly Library 1938a, b, c). The report of Rajewski and Timofeeff-Ressovsky (1939) on this topic would most likely have considerable scientific weight as Timoféeff-Ressovsky was on par with Muller for scientific reputation in the area of radiation genetics.

In the Atomic Energy Commission (AEC) manuscript by Uphoff and Stern (1947) concerning her replication of the Caspari study, the low response control group issue was explicitly addressed as follows in their "Discussion" section. "In his extensive studies on the effect of aging on the mutation rate in sperm, H.J. Muller (unpublished) has found a weekly increase of about 0.07 % for sex-linked lethals in various stocks kept at 25 °C. At 18 °C, the temperature used for aging in the laboratory, the weekly increases may be assumed to be slightly less, perhaps 0.05 %. Taking a value of 0.10 %, similar to that of Spencer and Stern's control rate, for sperm before aging, the expected control rate after aging should be approximately 0.25 %. This figure is much closer to the control rate observed by Caspari and Stern than to that found in the present work." In their acknowledgments of this manuscript, Uphoff and Stern stated that "we are very grateful to Dr. H. J. Muller for his permission to quote from his unpublished data." Thus, Muller would have known that his research was used to evaluate the reliability of the Caspari and Uphoff control groups. The control group response of Uphoff and Stern (1947) was sufficiently low such that they stated that the data were uninterpretable (i.e., "a final interpretation of these results cannot be offered."). Uphoff and Stern (1947) explicitly raised the possibility that the low control group values "may reflect a personal bias of the experimenter." The manuscript did not identify whether the bias concern statement was directed to Stern, Uphoff or both, or the type of bias. (2) Uphoff's second experiment also displayed a similarly aberrant low control group response, likewise affecting the possible utility of the data. (3) The third (and final) Uphoff experiment obtained control values in the normal range but an aberrantly high treatment response, even assuming a linearity dose response (see Calabrese 2011a for a detailed evaluation). "Appendix" section provides the temporal letter exchange between Stern and Muller on the key question of control group mutation frequency upon which the acceptance of the Caspari and Uphoff studies are based.

Muller (1950b) discredits the conclusion of Caspari and Stern (1948) by asserting that the control group values were unusually high. (1) Muller failed to state that the "high" control value of Caspari and Stern (1948) was first put forward as a criticism by Stern in the fall of 1946, when Caspari informed Stern that his findings supported a threshold, rather than a linearity interpretation. (2) He also did not report that Caspari successfully rebutted Stern by presenting data on control group responses from published studies in the literature and from unpublished data provided by Muller himself. Muller failed to state that he had published a summary of the mutation rate of sperm stored in the spermatheca for several weeks (Muller 1945). This is the information that he sent to Stern that supported the reliability of the Caspari control group data and marginalized the Uphoff study control group (see "Appendix" section). Later studies by Muller and his student Helen L. Byers at the University of Indiana also supported the Caspari control group mutation frequency (Byers 1954; Byers and Muller 1952). Nonetheless, Muller (1954b) would inexplicably continue his criticism of the Caspari and Stern (1948)

study, repeating the "unusually high control frequency" (page 476) conclusion as a basis to reject its challenge to linearity. The question may be raised as to why Muller would directly contradict himself on such a serious matter and never be exposed to criticism. While any answers to this question must be speculative, Sankaranarayanan and Wassom (2008) unequivocally state that Muller was an "unquestioned authority," suggesting that it would be quite difficult to challenge him or even consider doing so.

It should be noted that in early 1949, Muller became concerned that Robley Evans of MIT was publishing a paper in the journal *Science* on the mutagenic effects of ionizing radiation and the nature of the dose response in the low-dose zone. Muller had reviewed the manuscript prior to publication and was upset that Evans had given credibility to the Caspari and Stern (1948) paper. Muller wrote to Stern (Lilly Library 1949, February 5) requesting that Stern contact Evans and try to convince Evans to withdraw his support for the Caspari and Stern (1948) findings. There is no evidence that Stern did this based on correspondence records. However, it is possible that the subsequent attack of Muller (1950a, b) on the Caspari and Stern (1948) findings was stimulated by this Evans paper (1949) which would need to be "neutralized."

Muller (1954b) also further criticized the Caspari and Stern (1948) paper in a vague manner as being "more doubtful than the others on some other grounds" (page 476), which he never clarified. Such criticism may have referred to the fact that Uphoff and Stern (1947) introduced a modified method of counting sex-linked recessive lethals, one that was different than reported by Caspari and Stern (1948) and also different than Spencer and Stern (1948). Uphoff and Stern (1947) recounted (i.e., adjusted) the Caspari and Stern (1948) data with the new counting method in order for it to be as directly comparable to their study as possible. The results of those adjustments were deemed by Uphoff and Stern to be insignificant in their 1947 paper, resulting in control and treatment responses that were, in fact, even more similar than before the adjustment (i.e., without a treatment effect). The published paper of Caspari and Stern (1948) did not incorporate this adjustment (perhaps resulting in the veiled criticism of Muller 1954a, b), whereas the Uphoff and Stern (1947) manuscript presented the original and adjusted data; only these adjusted data were used for the Caspari and Stern (1948) data as summarized in the 1949 paper in *Science* by Uphoff and Stern. Regardless, the adjustment for differing lethality estimation techniques did not affect the study interpretation. In a letter on February 9, 1949, to Caspari in anticipation of the *Science* publication, Stern (American Philosophical Society 1949, February 9) stated that "It will be shown below (the *Science* manuscript) that the difference in defining a lethal is of no significance in the evaluation of the results."

In his 1950 papers, Muller never addressed any of these critical issues that might affect a decision on the nature of the dose response (Muller 1950a, b). He also failed to state that the Uphoff and Stern (1949) paper was only a one-page summary, has very low control group values, no presentation of research methods and that Uphoff and Stern (1949) promised to publish a detailed paper with all the missing methods and data but had not (and never did). By discrediting the Caspari and Stern (1948) paper and restoring the Uphoff data, Muller was able to protect his scientific reputation, his ethical standing and to give strong support to the linearity single-hit theory dose-response model.

In a second paper in 1950 entitled *Radiation Damage to the Genetic Material* in the *American Scientist*, Muller (1950b) used the findings of Stern and his colleagues to extend "the principle of proportionality of mutation frequency to dose down to doses of 50 r and 25 r and of less than 0.001 r per minute, with a time-intensity relation differing by over 400,000 times from that of our high intensity dose."

Comment

By using the now revitalized data of Uphoff, Muller made the claim of linearity over a 400,000-fold dose range. This was a major conclusion as it gave an assertion of linearity at low dose by a Noble Prize winner who had great authority within the field. Furthermore, Stern (1960) continued to affirm the findings of Uphoff and Stern (1949) in the second edition of his acclaimed genetics textbook, published in English, German, Japanese, Polish, Russian, and Spanish (American Philosophical Society 1973, November) (autobiographical statement), by stating that the dose rate had no impact on the mutation incidence in *Drosophila*, whether administered acutely or given "slowly and continuously, that is, 'chronically,' given over a long period." In order for Stern (1960) to have reached this conclusion, he had to diminish the findings of Caspari and Stern (1948) and accept those of Uphoff and Stern (1949). A further note is that the Muller (1950b) paper contradicted his 1950a paper on the dose rate: The two papers used a different lowest dose rate: 0.001 r/min (Muller 1950b) versus 0.00165 r/min (50 r/30240 min in 21 days) (Muller 1950a)—a 65-fold difference. Muller (1950b) rounded down the 0.00165 r/min rate to 0.001 r/min, increasing the extrapolation range from approximately 250,000- to 400,000-fold. Why Muller rounded the numbers down is not known, nor was it necessary. Secondly, if rounding was to occur it would normally have been rounded up to 0.002 r/min. This action of Muller reveals an effort to exaggerate the linear extrapolation range. Third, Muller (1950b) makes an error in his statement that the linearity was shown with a dose rate "less than 0.001 r per minute" when the actual value was 0.00165 r/min.

Table 1 Hermann J Muller and Curt Stern quotes on low-dose linearity

References	Quote
Muller (1948)	Page 462 "…the frequency of the mutations induced will be proportional to the total dose of radiation received over an unlimited period of time." "There is then absolutely no threshold dose, unlike what is true of many other biological effects of radiation, and even the most minute dose carries a definite chance of producing mutations—a chance exactly proportional to the size of that dose."
Muller (1952)	Page 317 "In making our calculations it is safe, as both the earlier (6–10) and the more recent (11–15) works have agreed, to accept the principle that the frequency of the gene mutations produced is simply (linearly) proportional to the amount of the total accumulated dose received, as expressed in r units. Moreover, as some of these same studies show, this relation holds within wide limits, regardless of how short and concentrated or dilute and protracted the exposure may have been, or whether it was given in one treatment or many." "There are good theoretical grounds for inferring that these principles hold true no matter how small the total dose, or the dose per unit time. Of course, such a sweeping conclusion necessarily involves an extrapolation from actual data. Not until recently has it been possible, because of technical difficulties, to test the mutagenic effectiveness of doses lower than about 13 r per day, totaling 400 r (11–13), and even the most recent work goes down no lower than about 2.5 r per day, totaling 25 r (14, 15)."
Stern (1950)	Page 433 "The proportionality rule has been proven to hold over a wide range. Figure 155 shows that, for Drosophila, the relation is essentially linear over the range from 25 r to several thousand r. It has further been shown that the frequency of induced mutations is independent of the time over which the radiation is applied."
Stern (1960)	Page 491 "It has been established for a variety of experimental organisms that the number of mutations induced by radiation is proportional to the dose. This proportionality has been proven to hold over a wide range of dosages. Figure 202 shows that, for Drosophila, the relation is essentially linear over the range 25–12,500 r (insects, unlike mammals, can survive after exposure to many thousands of roentgens). It would be desirable to extend the data toward dosages lower than 25 r, for instance, to 10 r, 5 r, and still lower. Since, however, the expected differences are small between the rate of mutations in not-artificially irradiated control organisms and that in organisms exposed to low artificial doses, it is difficult to obtain significant results even with large experiments."

Impact of the Stern and Muller deceptions

Effect on the radiation genetics literature/community

In the aftermath of his Nobel Prize Lecture, Muller published his Lecture in the *Journal of Heredity* in 1947 (Muller 1947), assuring its broader distribution. Within 4 months of the Noble Prize Lecture, he gave a lecture to the New York Academy of Medicine during which he affirmed his Nobel Prize Lecture message, stating that there was "absolutely no threshold dose" for mutations and that induced mutational response was proportional to the total dose (Table 1). This presentation was published in the Academy's journal (Muller 1948) soon thereafter. Stern (1950) also cited Spencer and Stern (1948) and Uphoff and Stern (1949) in his acclaimed textbook, emphasizing that the dose response for mutations was linear (Table 1).

These follow-up activities by Stern and Muller had an impact on other leading radiation geneticists influencing them to adopt the linearity dose-response interpretation. Table 2 provides a series of quotations from subsequent publications of leading contemporary radiation geneticists. The quotes are numerous, varied, and a fair representation of what each author stated. These comments strongly support the conclusion that there was a generally consistent view that the nature of the dose response in the low-dose zone for mutations was linear. Most of these quotes directly cite the research of Stern and his colleagues as providing the key evidence supporting linearity, especially that of Spencer and Stern (1948) and Uphoff and Stern (1949). This demonstrates the significance and success of the Stern mediated manipulation of the Caspari and Uphoff studies in affecting mutation dose-response beliefs of key research leaders of the radiation genetics community.

Effect on the BEAR I Committee/Genetics Panel

Crow (1995) noted the following in his historical recounting of the BEAR I Committee Genetics Panel: "the debate over the nature of the dose response for ionizing radiation and mutations had been decided before the convening of the BEAR Committee in November 1955." The accepted view was clear and unified; the answer for the dose response question for mutagenicity was "linearity at low dose."

When reading the transcripts of the BEAR I Committee Genetics Panel, one is struck by the absence of debate and even discussion on the issue of dose response (e.g., linearity vs. threshold). To illustrate the fact that the decision on

Table 2 Radiation genetics quotations about the mutation dose-response following Hermann J Muller's Nobel Prize and Curt Stern's (with Spencer, Caspari and Uphoff) mutagenicity papers

References	Quotes
Catcheside (1950)	Page 592 "The induced mutation is proportional to the total dose over the whole range investigated, down to total doses as small as 25 r. There is good reason to conclude that there is no threshold dose, i.e., no dose so small that it gives no mutational effect. Also, the intensity of the radiation appears to be without effect on the frequency of mutation induced by a given total dose. A dose of 50 r given in a fraction of a minute appears to give no greater effect than the same dose given in the course of a few weeks. There is no threshold, no time factor, and no recovery, the effects being cumulative."
Glucksmann (1950)	Page 42 "The induction of gene mutations is linearly proportional to dose even down to levels of 25 r (Spencer and Stern 1948)."
Lefevre (1950)	Page 341 "It has been amply verified that the number of mutations produced by X-rays is linearly proportional to the total dose applied, even when the total dose received is very small (see Spencer and Stern 1948). Further, the number of mutations produced is independent of the rate of dosage (Uphoff and Stern 1949)."
Sax (1950)	Page 332 "The early work by Muller and by Timoféeff-Ressovsky showed a linear relationship between X-ray dosage and mutation frequency in *Drosophila*. It was also found that the induced mutation rate was independent of radiation intensity. From these observations it was concluded that the X-ray-induced mutations are produced by single 'hits,' and that there is no threshold effect. Spencer and Stern (2) found no increase over the spontaneous mutation rate by irradiating *Drosophila* for 21 days at 2.5 r/day, but later experiments by Uphoff and Stern (3) indicated that low intensities are effective."
Higgins (1951)	Page 9 "As a result of exhaustive experiments on the genetics of the fruit fly, of mice and of many plants, it is held that the number of induced mutations bears a linear relationship to the total amount of radiation absorbed by the sensitive volume of the cell and is independent of either the duration or the intensity of exposure. Consequently, a long exposure to low-level radiation would have the same genetic effect as shorter exposure to a higher level. Experiments of Spencer and Stern (1948) on the fruit fly show that the percentage of sperm containing a sex-linked lethal mutation is increased about .002 per r of radiation exposure and that 50 r exposure is required to double the natural mutation rate." "Spencer and Stern (l.c.) conclude their exhaustive study of the validity of the linear relationship between radiation exposure and mutation frequency with the statement (p. 64): '…for radiation with X-rays, dosages as low as 25 r produce mutations as drastic in their effects and in the same proportion to the dosage as do exposures to high dosages. If an extrapolation is permissible, one may assume that there exists no tolerance dose below which mutations are not induced." "The classical hit theory of induction of mutations, particularly the linear relation between dosage at low levels and mutation rate, has been questioned by Caspari and Stern (1948), who found no significant difference in mutation rates in the sperm of the fruit fly between controls and experimentals exposed to 2.5 r per day for 21 days. Uphoff and Stern (1949), however, after further tests, concluded that low-level radiation does produce mutations in fruit-fly sperm and that the apparent inconsistencies of previous results were due to different experimental techniques and errors in sampling."
Stone (1952)	Page 657 "There is no threshold for genetic mutations…" (cited Muller reference 1950, J Cell Comp Physiol 35(suppl 1):9–70.)
Singleton (1954a)	Page 598 (Discussion) "That a non-linear relationship exists between dose rate of chronic gamma radiation and mutation rate of endosperm characters seems to have been well established by these experiments. This was shown quite conclusively by disproportionately higher mutation rates at the higher dosages, and was definitely indicated by the fact that there seems to be a threshold of dosage required to raise the mutation rate from the spontaneous level to a detectable increase over that level." Page 599 "These data (i.e., data shown in Singleton 1954a study) showing a definite threshold are in contrast to the Drosophila data of Spencer and Stern (1948), where no threshold was indicated even when low doses of radiation were used. In their experiments the effects of acute radiation were studied. Caspari and Stern (1948), studying chronic gamma radiation, found no increase over the controls for doses of 2.5 r/day for 21 days. However, it was later demonstrated by Uphoff and Stern (1949) that the controls used by Caspari and Stern had an abnormally high sex linked lethal frequency and that actually there was an effect of the chronic gamma radiation of 2.5 r/day."
Kelner et al. (1955)	Page 36 "The linear mutation-dose curve indicated for X-ray induced drosophila lethals (Lethals-Dros:X) is perhaps best exemplified by the data of Spencer and Stern (53) for sex linked lethals and may be considered as the classical type of mutation-dose relation. Interpreted within the target theory, the linear relation indicates that a single hit is sufficient to produce a mutation."

Table 2 continued

References	Quotes
Nybom et al. (1956)	Page 81 "In this connection references may be made to the concordant results of Uphoff and Stern (1949) who did not find any threshold in *Drosophila* after low dose rates. A similar result was published by Sax (1950) using chronic irradiation of *Tradescantia* pollen."
Lewis (1957) (This Science article was reprinted in Congressional Testimony)	Page 971 (columns 2 and 3) "Gene mutation has long been known to show a linear relationship with respect to dose of ionizing radiation from studies with *Drosophila*. This linearity has been extended by Spencer and Stern (43) to doses of 50 and 25 roentgens. Gene mutation is also known to be directly proportional to the accumulated dose of radiation, even when the radiation is chronically administered at a relatively low dose rate, as in the studies of Uphoff and Stern (44)."
Norwood (1958)	Page 1929 "Several geneticists[4] have sketched the background which has lead to the concern of this study. Briefly, realization that radiation increases the mutation rate dates back 30 years to Muller's experiments with fruit flies[4e]. Spencer and Stern,[5] using more than 50 million flies, showed that genetic damage was proportional to dosage in the important range of 25 to 50 r. Concern has been heightened by recent findings[4f] that exposure of mice to a given quantity of radiation increases the mutation rate by about 15 times as much as does an equal exposure of Drosophila, which had formerly served as the sole basis for inferring human risks."
Spear (1958)	Page 20 "There is general agreement, however, that mutations can be produced with very low dosage down to a level which approaches natural background (Uphoff and Stern 1949)."
Newcombe (1960)	Page 331 "One basic premise which has not so far been seriously challenged is that the number of gene mutations resulting from irradiation varies in direct proportion to the dose. In other words, there is no threshold level of radiation below which the mutations will not be produced." "In the fruitfly the curve has, by dint of considerable work, been pushed to within 25 roentgens of the origin (Caspari and Stern 1948; Spencer and Stern 1948; Uphoff and Stern 1949) (3, 4, 5)."

LNT had already been settled prior to the creation of the BEAR I Committee, there was no discussion of the scientific foundations of the LNT, including any documenting of its theoretical basis and experimental support, including its strengths and limitations. As noted above, the Genetics Panel placed a high priority on the chronic exposure experiments published under the leadership of Curt Stern. Yet these studies, even ignoring the control group problems of the Uphoff and Stern experiments, had little or no risk assessment relevance. That is, these were sex-linked recessive lethality studies in which the spermatozoa were deposited in the spermatheca of the female. The females were then placed into a type of specialized experimental "hibernation" in which there was a profound alteration of the diet and a lowering of the temperature, changes designed to prevent egg production. The females (with the deposited spermatozoa) were then exposed for 21 days (24 h/day) to gamma irradiation. After the 21 days, the dietary and environmental conditions were changed to permit egg laying so that the testing for sex-linked recessive lethal mutations could take place. In effect, Stern exposed the spermatozoa to ionizing radiation for the equivalent of an entire lifespan, something comparable to a 70–80-year human lifespan. The spermatozoa are known to be highly compromised, having lost much of their normal repair capability. The study represented a worse case exposure scenario, that is, selection of a very susceptible developmental stage linked to a profoundly extended and highly unrealistic exposure period. In effect, the study was a chronic exposure to a cell type that has only a very short developmental stage. The basic concept of the study was not appropriate for a chronic exposure with risk assessment application. The BEAR I Committee incorrectly accepted Stern and Muller's concept of "chronic" for risk assessment purposes as did the entire field and regulatory agencies.

While the BEAR I committee relied upon the findings of the *Drosophila* research directed by Curt Stern, it failed to cite other similarly large-scale *Drosophila* studies (Bonnier and Lüning 1949; Bonnier et al. 1949) in which the lowest total dose was 8 r, below the lowest dose (25 r) of the Spencer and Stern (1948) findings. These papers documented the response of several single genetic loci (e.g., white and forked loci) to which their detailed statistical analysis for mutational studies was applied. The analysis revealed a linear dose response in the dose range of 700–2,800 r, whereas the linearity response was not observed in the low-dose range (8–16 r), where the data were supportive of a threshold response. The authors also suggested that the difference in the shape of the dose response between high and low doses was indicative of differing dose-dependent mechanisms. At the high doses, the linear dose response was consistent with the target theory of Timoféeff-Ressovsky et al. (1935), whereas at lower doses mutational effects could be due to the effects of chemical

mutagens (i.e., hydroxyl radicals from the hydrolysis of water). The dose-dependent mechanism-based hypothesis of Bonnier and colleagues (Bonnier and Lüning 1949; Bonnier et al. 1949) was soon supported with experimental data (Haas et al. 1950; MacKey 1951; Lüning 1954; Barron 1954). According to Barron (1954), "it is dangerous, however, to extrapolate from experimental data with large doses of radiations to what might take place with small doses. In biological systems the effect of ionizing radiations differs qualitatively when the radiation dose is changed. Small doses act by indirect action and produce mainly oxidations. Large doses act by two mechanisms," that is, free radical formation via water hydrolysis and by a direct collision, which is consistent with the target theory.

The Bonnier and Lüning (1949) (Bonnier et al. 1949) papers were also critical of the use of sex-linked recessive lethal experiments for estimating responses in the low-dose zone due to the "impossibility of differentiating between true lethals and semi lethals, and the fact that there are several hundreds of targets per chromosome ready for lethal mutations…" The lack of target specificity would represent an important limitation in the interpretation of dose-response relationships and their potential application to a mechanism-based risk assessment process. Bonnier et al. (1949) also provided a detailed statistical reanalysis of the Spencer and Stern (1948) data challenging the broadly accepted conclusion that the linearity response applied across the entire dose-response range, including the lower dose range. None of these fundamental technical issues were discussed by the BEAR I committee.

Another relevant aspect of the discussion on the nature of the mutation dose response involved the research of Arnold H. Sparrow and W. Ralph Singleton of the Brookhaven National Laboratory. Chairman Warren Weaver introduced their research and its relevance to the BEAR I Committee/Genetics Panel (Weaver W., February 5–6, 1956, see page 110—Transcript) (BEAR I 1956). The discussion of the Sparrow and Singleton data was then led by Committee member Berwind D. Kaufmann, who claimed to have copied several tables from their paper. He stated that Sparrow and Singleton showed that 0.41 r per day yielded a modestly elevated (i.e., less than twice the control values) but statistically significant effect on micronuclei formation. What Kaufmann failed to inform the Committee was that Sparrow and Singleton (1953) specifically stated that a threshold response had been observed at a lower dose. In fact, there was no discussion concerning their threshold dose-response statement by the BEAR I Committee/Genetics Panel. The data in Table 2 (page 35) of the published paper by Sparrow and Singleton (1953) show that 0.084 r per day caused no significant increase in micronuclei. This recounted activity of the BEAR I Committee/Genetics Panel demonstrates that it either ignored or was misled on the published findings of Sparrow and Singleton as the data did not support the pre-determined linear dose-response conclusion. This analysis also suggests that the BEAR I Committee/Genetics Panel was very selective in their choice of what data to consider and that such decisions reveal a prevailing bias supportive of LNT model acceptance.

Since 0.41 r per day of radiation in the Sparrow and Singleton (1953) hypothesis study is more than 1,000 times greater than the naturally occurring intensity, these data do not support the theory that the spontaneously occurring micronuclei are produced by naturally occurring ionizing radiation. The findings of Sparrow and Singleton (1953) were similar to that of Giles (1940) from Harvard who showed that when *Tradescantia* were "subjected to irradiation 1,000 times that due to natural radiation….no increase in aberration was found." Other experiments by Giles indicated that even using ionizing radiation at some 1,800-fold above background no impact on the occurrence of spontaneous mutations occurred.

It is possible to obtain a sense of the personal views of a number of the members of the BEAR I Committee/Genetics Panel on the matter of dose response via two contemporary publication avenues: Testimonies at a 1957 Congressional Hearings (Table 3) and journal publications in the open literature (Table 4) such as a special issue of *Scientific American* on ionizing radiation and several other journals. Based on these collective comments, it follows that the BEAR I Committee/Genetics Panel report and an article in the journal *Science* (Table 5) summarizing the report of the Genetics Panel were replete with statements asserting linearity at low dose.

Placing the new Muller and BEAR I Genetics Panel developments in perspective

The story of Muller's Nobel Prize Lecture is important for its history of science implications, as well as its role in affecting the decision of the US National Academy of Sciences (NAS) to recommend a linearity dose-response policy for assessing risks to the genome from ionizing radiation, replacing the threshold dose-response model. This formal recommendation initiated a series of advisory and regulatory dominoes in essentially all countries to adopt linearity and apply it to somatic effects, that is, cancer risk assessment, for ionizing radiation and later for chemical carcinogens (Calabrese 2009). The linearity decision of the NAS BEAR I Committee/Genetics Panel was strongly championed by Muller, the titular leader of radiation geneticists and with strong ties to all radiation geneticists on the BEAR I Committee/Genetics Panel. In fact, the switch to linearity, which was ushered into the international

Table 3 BEAR I Committee Genetics Panel member quotes at Joint Committee on Atomic Energy—1957

References	Quotes
Muller (1956)	Page 392 "In material of varied kinds, but more especially in *Drosophila*, there is good evidence that over a considerable range of dose (in *Drosophila*, from some 50 r to more than 1,000 r, a more than 20-fold range) the frequency of point mutations (like that of chromosome breaks) is directly proportional to dose."
Crow (1957a)	Page 1013 "4. Evidence from experimental animals, principally Drosophila, indicates that the number of mutations produced is strictly proportional to the amount of radiation received. There are departures from this straight-line relationship at high doses, but these are too high to be likely to be encountered in any ordinary human situation. It is technically impossible to test this relationship for the very lowest doses, but the straight-line relation holds down to the smallest amounts that have been studied." "For these reasons a simple proportionality between the amount of radiation and the number of mutations is fully accepted by geneticists." "The proportionality between dose and mutation production holds irrespective of the intensity or spacing of the dose." Representative Holifield (page 1013) questions Dr. Crow: "This, then, would establish as far as the majority of the geneticists are concerned the principle of linear progression in deleterious effects of radiation regardless of amount?" Dr. Crow answers: "That is correct. A nonthreshold situation, to put this in yesterday's vocabulary." "This means that there is no such thing as a safe dose of radiation to the population. Any amount of radiation, however, small, that reaches the gonads—testes or ovaries—of a person who may later reproduce, involves a risk proportional to that amount."
Glass (1957a)	Page 1030 "The data are most extensive for the fruitfly and the lowest dose that has actually been studied is 25 r." Page 1031 "Because a mutation can be produced by a single ionization in the right place, there is no threshold below which the amount of radiation is too small to produce mutations—that is, every dose produces mutations with a probability equal to its magnitude." "This is to repeat what Dr. Crow said, that there is no safe dose of mutation. This curve continues down without any threshold until it hits the zero point…"
Muller (1957a)	Page 1052 "In respect to the fact that probably there is no threshold, that these effects are proportional to the dose, in this respect these effects of radiation—and also the leukemia—on the exposed individual himself resemble those produced by the radiation in weakening descendants." "You have heard Dr. Glass and Dr. Crow say that geneticists are convinced that there is no threshold for the genetic effects and that others, too, now accept that principle for the genetic effects." "If this is true of these other effects, and it is certainly time we knew whether it was—I think the evidence is convincing that it is—then this important resemblance between the effects on later generations and on the exposed generation is probably not an accidental resemblance. For there is growing reason to infer that this shortening of life and the other long delayed damage done to an exposed individual have their basis in damage done to the genetic material—the chromosomes and their contained genes—of the body's ordinary cells, those of the blood, skin, glands, and so forth, similar to the damage done in his reproductive cells that is passed on to later generations." Page 1056 "Through work on the fruitflies where we have the most exact knowledge to date, unless Dr. Russell has more exact knowledge on mice now, we can get a kind of minimum estimate of the amount of damage to the children by a given amount of irradiation of the parents."
Muller (1957b)	Page 1066 "Since there is much evidence indicating a linear relation between the radiation dose and the frequency of the induced point mutations, even at extremely low doses, and the exactly cumulative nature of these radiation effects, it becomes possible to arrive at probable estimates of the minimum damage done to subsequent generations by any given chronic or acute exposure of parents." Page 1067 "…leukemia and some other malignancies, the induction of which may also be linearly dependent upon radiation dose…"
Joint Committee on Atomic Energy (1957)	Page 12 "…geneticists believe that the direct proportion applied down to zero dose—that is, that there exists no safe "threshold" below which the dose produces no damage, and that damage occurs from any irradiation of the genetic cells, no matter how small the dose."

Table 4 BEAR I Committee Genetics Panel member quotes on low-dose linearity in journals after the BEAR I Committee

References	Quotes
Crow (1957b)	Page 19 (column 2) "2. The number of mutations produced is directly proportional to the dose in roentgens. The linear proportionality over wide dose ranges has been shown in several organisms, especially in *Drosophila*." "Experimental verification in *Drosophila* has been carried to as low as 25 r…" Page 20 (column 1) "The proportionality between dose and mutation production holds irrespective of intensity or spacing,…" Page 20 (column 2) "The conclusions of the previous section imply that there is no such thing as a "safe" dose. Any increase in radiation, however, small, involves a risk proportional to that amount."
Glass (1957b)	Page 956 "Our present evidence indicates that the frequency of these point mutations always increases linearly with the radiation dose (Fig. 1). In Drosophila studies this holds over the range from 25 r to 6,000 r. In some plants, the linear range has been extended down to about 5 r. In mice, the linearity in relation to dose holds over the range from 300 r to 600 r, and there is no sign that it does not hold at lower doses. This linear proportionality to dose, over and above the spontaneous frequency of mutation, implies that (a) as long as dosage is measured in terms of roentgens, that is, in terms of the ionization produced by the radiation, absorbed quanta do not interact to produce effects, but are individually effective; and (b) there is no sign of a threshold dose below which mutations are not produced. Rather, even the lowest doses are proportionally mutagenic, and all doses, however, distributed, are additive or cumulative in effect."
Beadle (1959)	Pages 225 and 226 "…thus there is probably no threshold below which radiation will produce no mutations. Since there is no repair mechanism, once the mutation process is complete, mutations induced at different times will tend to accumulate in a line of descent…"
Hollaender and Stapleton (1959)	"In sum, cell studies have served to elucidate the basic mechanism by which ionizing radiation damages the living organism. They have provided no evidence that there is a true threshold of dosage below which ionizing radiation produces no harmful effects…"

community by the BEAR I Committee Genetics Panel, is the most significant action in regulatory environmental public health history with ever expanding social, political, economic, and public health implications (Hamblin 2007).

The present paper provides the first documentation of how Muller (Muller 1950a, b, 1954a, b) himself used the carefully constructed activities of Stern (described in detail in Calabrese 2011b) to enhance the concept of linearity and to protect his reputation. Muller lent credibility to the technical note of Uphoff and Stern (1949) while further marginalizing the Caspari and Stern study results (Caspari and Stern 1948). The stakes were high on multiple levels and these core individuals knew it. Stern and Muller needed to prevent the acceptance of the Caspari and Stern (1948) study findings in order to sustain the single-hit linearity model. They also needed any criticisms of the Spencer and Stern (1948) and Uphoff and Stern (1949) papers to be muted. They were successful as other leaders of the radiation genetics community simply failed to address the serious limitations of the Spencer and Uphoff findings while incorrectly asserting that the Caspari and Stern (1948) paper suffered from an aberrantly high control value, simply re-stating the demonstrably incorrect, but authoritative conclusion of Muller (1950a).

Despite the fact that Caspari had successfully rebutted the first challenge of Stern concerning the control group spontaneous mutation rate, there is no evidence that he disputed the control group mutation rate reversal decision of Stern barely a year later and of Muller's equally strange affirmation of Stern's position as well (Muller 1950a, b). A January 27, 1949, letter from Caspari to Stern supported the publication of the Uphoff and Stern (1949) paper now adopting part of the mantra of Stern, that is, that there is considerable variability in the mutagenic frequency of sperm prolongedly stored in the spermatheca. This conclusion provided the opportunity to rehabilitate the inexplicitly low control group values of Uphoff. Caspari, however, would not go so far as to also state that his control values were unusually high. At the time of the Uphoff and Stern (1949) article, there were only two papers published in the literature (Rajewski and Timofeeff-Ressovsky 1939; Kaufmann 1947) on aged sperm and mutation and the published abstract of Muller (1946b). Each supported the mutation frequency of Caspari. These findings are consistent with subsequent mutation frequencies in aged sperm stored in the spermatheca of female Drosophila (Byers 1954; Byers and Muller 1952; Rinehart 1969; Graf 1972; Muller et al. 1961). Muller et al. (1961) stated that "The data clearly showed a rise in mutation frequency (averaging some .06 percent of recessive lethals in the X chromosome per week) resulting from storage of the mature spermatozoa in the female" (page 213). Note the striking similarity of how

Table 5 Low-dose linearity quotation in the journal Science from article summarizing the findings of the BEAR I Committee Genetics Panel

References	Quotes
BEAR I (1956)	Page 1159 (column 2) "…the genetic damage done, however, felt and, however, measured, is roughly proportional to the total mutation rate." Page 1160 (column 1) "3) Any radiation dose, however, small, can induce some mutations. There is no minimum amount of radiation dose, that is, which must be exceeded before any harmful mutations occur." Page 1160 (bottom column 1) "The probable number of additional induced mutations occurring in an individual over a period of time is by and large proportional to the total dose of extra radiation received, over that period, by the reproductive organs where the germ cells are formed and stored." Page 1160 (top column 2) "The *total dose* of radiation is what counts, this statement being based on the fact that the genetic damage done by radiation is *cumulative*." Page 1162 (column 2)—how harmful are radiation-induced mutations? "1) Thus the first and unanimous reply to the question posed by the title to this section is simply this: *Any radiation is genetically undesirable*, since any radiation induces harmful mutations. Further, all presently available scientific information leads to the conclusion that *the genetic harm is proportional to the total dose*… This tells us that a radiation dose of 2X must be presumed to be twice as harmful as a radiation dose of X…" Page 1164 (column 1) "…for there is no such figure other than zero." [referring to whether there is an amount of radiation which is genetically harmless (preceding phase)] Page 1164 (column 1) "As geneticists we say: keep the dose as low as you can." Page 1165 (last sentence) "From the point of view of genetics, they are all bad." (referring to the effect of exposures to ionizing radiation)

Uphoff and Stern (1947) characterized Muller's data some 14 years earlier, "a weekly increase of about 0.07 %…" The 0.06 % increase would yield an estimated 0.28 % (i.e., 0.06 % × 3 weeks + 0.10 % background = 0.28 %) mutation incidence after 3 weeks, consistent with the Caspari and Stern (1948) findings, the logic used in Uphoff and Stern (1947) and with the Muller (1946b) statement that "spermatozoa aged several weeks in the female may contain several times as many mutations as they originally had." Furthermore, the reported inter-study variability for mutations of aged sperm and/or stored sperm aged in the spermatheca appears modest with 95 % confidence intervals typically being about ±25–30 % of the mean. The attempt by Stern, therefore to assert that the very low values of Uphoff reflected a highly variable response endpoint was not supported in the contemporary and subsequent literature. Stern never argued his case by a comparative data assessment nor did he address the apparent contradiction with the Muller data and comments which he (i.e., Stern) previously used when he concluded that the Caspari data were credible while those of Uphoff were not. He simply made an authoritative declaration that was accepted without question or comment by the radiation genetics community.

BEAR I Committee/Genetics Panel

The BEAR I Committee/Genetics Panel was comprised of outstanding scientists and national leaders. Despite their significant individual accomplishments in scientific and radiation genetics domains, the committee as a whole lacked extensive experience in conducting low-dose, dose–response studies. Only two of the members had extensive direct experimental dose-response experience (i.e., Demerec and Russell) up to the time of the BEAR I meetings. This experience was essential for evaluating the nature of the dose response in the low-dose zone. Of these two, Demerec had the most extensive and varied experience having dealt with multiple models and agents as well as different types of radiation. His research experience on dose response was spread over a 25-year period starting about 1931. Nonetheless, his dose-response experience with *Drosophila* was limited to only a few high dose studies during the 1930s, a key limitation. Despite his significant and prolonged career at Oak Ridge, Russell was relatively new to the dose-response research area, with about 5–6 years experience at the start of the BEAR I Committee in 1955. In the case of Russell, his developing research findings with mice were still somewhat premature, having little impact on BEAR I Committee/Genetics Panel conclusions. Among the remaining members of the committee, Muller's principal dose-response experience is found in the research of Hanson and Heys (1929), and Oliver (1930, 1931) at the University of Texas and Ray-Chaudhuri (1944) at Edinburgh (completed in 1939), as well as his consultant role with Stern from 1943 to 1946. Limited relevant low dose-response research based on the publication record experience was found for Berwind Kaufmann. Alexander Hollaender, PhD in physical chemistry, had made

important contributions on the effects of UV wavelengths specificity on mutation in bacteria and fungi. He became the director of radiation biology research at Oak Ridge, hiring Russell. Hollaender had no experience with Drosophila research. H. Bently Glass' low-dose experimental research experience was quite limited during BEAR I, becoming far more extensive only after BEAR I. Importantly, very limited to no meaningful dose-response research experience is apparent for the remaining 11 members [George W. Beadle, Charles W. Cotterman, James F. Crow, Gioacchino Failla, Clarence C. Little, James V. Neel, Tracy M. Sonneborn, Alfred H. Sturtevant, Sewall Wright, Warren Weaver (Chair), and Shields Warren] of the BEAR I Committee/Genetics Panel. This situation resulted in the "senior" dose-response experience to reside with Demerec and Muller, two individuals on record to save the "hit" model.

The geneticists on the BEAR I committee were principally basic researchers; their experimental approaches were neither dose response nor risk assessment oriented. Even Muller (1950a, b) claimed that the work of Spencer and Uphoff (with Stern) at low doses would markedly extend his and his students' (e.g., Hanson and Oliver) research conducted at very high doses. Further, in the detailed comments that Muller sent to Stern about the Spencer (Lilly Library 1946, September 13) and Caspari (Lilly Library 1947a, January 14) manuscripts, nearly all dealt with fundamental biological/genetic questions with little direct relevance to risk assessment. Multiple study design issues and other methodological/analysis problems documented in Calabrese (2011b) for the Spencer and Stern (1948) paper were not identified by Muller (Lilly Library 1946, September 13). The members of the BEAR I Committee/Genetics Panel looked to Muller for leadership on matters related to the dose–response. However, Muller displayed critical limitations in assessing such studies based on his written statements. Thus, the methodological and analysis limitations of the Spencer and Stern (1948) paper and the serious flaws of the Uphoff and Stern (1949) paper were missed by the radiation genetics community and the BEAR I Committee/Genetics Panel, a condition that continues (Lipshitz 2005). Of further note is that Muller (1946b) and Kaufmann (1947) published findings on the control group mutation rate of aged *Drosophila* sperm that supported the findings of Caspari and Stern (1948). Kaufmann worked closely with and under the direction of Demerec at Cold Spring Harbor at that time. Furthermore, an October 7, 1947, letter (i.e., 6 weeks before submitting his paper to *Genetics*) from Caspari to Stern (American Philosophical Society 1947g, October 7) stated that "I have discussed the paper (the Caspari/Stern manuscript) with Demerec and Kaufmann. Both did not find very much to suggest……Both Demerec and Kaufmann were impressed by the amount of material which we have. The ageing effect in our experiments is of the same order of magnitude as that found by Timoféeff and Kaufmann." In fact, Caspari and Stern (1948) cited a 1947 paper by Kaufmann as support for control group values of their study. Muller and Kaufmann, both BEAR I committee members, therefore, reported research on mutation incidence of *Drosophila* aged sperm findings consistent with the findings of the Caspari and Stern (1948) paper. Thus, the BEAR I Committee/Genetics Panel should have been informed on the issue of control group validity by Demerec, Kaufmann, and/or Muller as it related to the research of the Caspari and Uphoff studies. However, based on the transcripts of the BEAR I Committee/Genetics Panel, Demerec, Kaufmann and Muller did not provide this information. Knowledge of the mutation rates in aged *Drosophila* sperm should have led to a reconsideration of the Caspari and Stern (1948) paper as well as generated serious questions about the findings and interpretations of the Uphoff and Stern (1949) data. This was a key issue affecting which study would be relied upon by the BEAR I committee. By their actions, the BEAR I committee Genetics Panel came to the erroneous conclusion that the Caspari study was unreliable due to its "unusually high control group value."

The future of ionizing radiation risk assessment was largely determined by the actions of a few, by the failure of the scientific community, especially the radiation genetics community, to probe deeper into the key findings of Stern and his colleagues and journals such as *Science* that published influential but poorly documented findings (Uphoff and Stern 1949). As has been pointed out, the linearity paper of Spencer and Stern (1948) was burdened with numerous methodological limitations that only recently have been documented, as well as statistical analysis limitations that challenged the conclusion of linearity at low dose (Bonnier and Lüning 1949; Bonnier et al. 1949) while the Caspari and Stern (1948) findings supporting a threshold perspective were unfairly marginalized (Calabrese 2011b). Furthermore, the BEAR I Committee/Genetics Panel failed to require Stern to provide the promised detailed accounting for the *Science* article (Uphoff and Stern 1949) upon which they so heavily relied.

According to Muller (1950a, b), by 1950, the radiation genetics community had accepted the linearity risk assessment paradigm (Table 2). Their belief was based largely on the fruit-fly work of Stern and his associates as well as the leadership, prestige, and authority of Muller, as few of the geneticist members of the BEAR I Committee/Genetics Panel had relevant experience with low-dose research. By the time, the National Academy of Sciences BEAR I Committee/Genetics Panel convened, therefore, the decision over the nature of the response in the low-dose zone had been decided by the radiation genetics community as there was no dispute or even debate within the BEAR

I Committee/Genetics Panel over the adoption of linearity to replace the threshold model for germ-cell mutagenicity (Crow 1995). The actions of Stern and Muller had led the way, assuring that the ends (i.e., linearity) justified the means (i.e., unfair/improper scientific evaluation). In fact, it is from this heritage and upon this foundation that regulatory cancer risk assessment theory and practice in the USA and throughout the world was built.

Conclusions

1. This paper provides specific documentation of how Hermann J. Muller supported and extended the like actions of Curt Stern to prevent the scientific community from discovering Muller's Nobel Prize lecture deception and to promote his ideological goal of linearity at low dose for ionizing radiation risk assessment (Table 6).
2. Muller strengthened the questionable actions of Stern in key publications in early 1950s while improperly discrediting the threshold findings of Caspari and supporting the "uninterpretable" data of Uphoff to achieve a linearity interpretation. The bases of these actions are documented in this paper.
3. The paper shows how the actions of Stern and Muller affected numerous publications and the dose–response beliefs of leaders of the radiation genetic community and the NAS BEAR I Committee/Genetics Panel, affecting the adoption of linearity at low dose for ionizing radiation-induced mutation and eventually for carcinogen risk assessment for ionizing radiation and chemical carcinogens.
4. The findings demonstrate that the adoption of the LNT model for risk assessment lacked a proper scientific foundation, yet was accepted by regulatory and public agencies worldwide.

Unresolved issues

1. Why didn't Stern publish the follow-up detailed paper containing the entire methodology for all the relevant data for the Uphoff three experiments?

Table 6 A summary concerning Muller's actions that affected the discrediting of Caspari's findings and acceptance of the Uphoff and Stern conclusions

A five-page detailed letter sent from Muller to Stern dated January 14, 1947, concerning scientific strengths and limitations of the Caspari and Stern manuscript provided no comment on the control group lethality data
Muller was actively researching the area of spontaneous mutations in sex-linked recessive lethality studies using aged sperm stored in the spermatheca of female fruit flies. This was the research method of the Caspari and Stern paper. Muller had been doing extensive research on this topic since the early 1940s. He was a leading authority on the topic
Muller provided his spontaneous control group data to Stern ("Appendix" section) in order to address the concern that Stern expressed about the apparently high control group values of Caspari
Based on the data of Muller, Uphoff and Stern (1947) determined that the average weekly spontaneous mutation rate in *Drosophila* sperm stored in the spermatheca of the female was about 0.07 %, yielding an additional mutation increase in about 0.21 % by 3 weeks, the length of the Caspari sperm storage time. The 0.21 % increase would be added to a background value of about 0.10 %, yielding an estimated control group value of about 0.31 %. The 95 % confidence intervals were about ±0.07 %, with an approximate range of 0.24–0.38 %. The values were obtained when studies were conducted at about 25 °C. At the lower temperature of 18 °C used by Caspari, it was estimated by Stern (and Uphoff) that the rate of increase might be reduced to 0.05 % per week. This would result in an estimated value for the Caspari control of about 0.25 %, nearly identical to his final adjusted value (i.e., 0.2489 %)
Based on these data, Uphoff and Stern (1947) concluded that the Muller data supported the Caspari conclusion that his control data were well within the normal range and not unusual or aberrant. The Muller data lead Uphoff and Stern (1947) to conclude the Uphoff findings were uninterpretable
Continued research in the area of spontaneous mutation in sperm stored in the spermatheca by Muller and his graduate students at the University of Indiana were consistent with this conclusion and quantitative assessment (Byers 1954; Byers and Muller 1952; Graf 1972). These findings were also consistent with that published by other researchers as well (Kaufmann 1947; Rinehart 1969)
Based on this information, the statements of Muller that Caspari's control group data were unusually high are inconsistent with: (1) His own data and that published by other researchers; (2) his previously detailed assessment of the Caspari data; (3) how Uphoff and Stern (1947) evaluated the Muller data, an evaluation that Muller was knowledgeable of, based on an acknowledgment in the Uphoff and Stern (1947) paper, and (4) internal written correspondence between Stern and Caspari
This assessment indicates that Muller's statements that Caspari's control group data were unusually high and adversely affected Caspari's threshold interpretation are contradicted by the body of evidence
While Muller repeatedly challenged the credibility of the Caspari findings by attacking his control group data, he made no statement about the reliability of the extremely low control group data of Uphoff. In fact, he would consistently cite the Uphoff and Stern (1949) paper as being a critical reference to support a linearity perspective
The collective findings on these matters indicate that Muller displayed compromised scientific judgment, having a significant impact on the scientific literature and national and international risk assessment policy that continues to the present

2. Why didn't the radiation geneticist community demand that Stern publish these findings?
3. Why didn't Stern address the scientific basis, if any, of why he reversed his position on the Uphoff control group data?
4. Why didn't Caspari challenge any of the multiple papers that claimed that the Caspari control group data were unusually/abnormally high or that their paper displayed "different techniques" or had "errors in sampling" that accounted for their threshold-like findings?
5. Why did Muller agree to let Uphoff and Stern (1947) acknowledge the use of his aged sperm data that supported the Caspari control groups findings and then repeatedly claim that Caspari's control group values were unusually high, adversely affecting the credibility of this paper?

Acknowledgments The research on the topic of hormesis has been supported by awards from the US Air Force and ExxonMobil Foundation over a number of years. Sponsors had no involvement in study design, collection, analysis, interpretation, writing, and decision to submit.

Conflict of interest The author declares that there is no conflict of interest.

Appendix

Stern–Muller temporal letter exchange concerning the aged-stored sperm control mutation rate (Source: Lilly Library, Stern–Muller correspondence)

Curt Stern wrote a letter to Hermann J. Muller on January 22, 1947 (American Philosophical Society 1947a), informing him that "At the present time it looks as if our new control data (probably the results of the first 3 months of the first Uphoff experiment; note that her first month's reading was an especially low mutation rate of 0.005 %) for aged sperm are considerably below those of Caspari's." He then asked Muller to "send me your figures on rate of sex-linked lethal in sperm aged several weeks, (most desirably, if you have them, data on 3 weeks), in comparison to control data from non-aged sperm?"

On February 3, 1947 (Lilly Library 1947b, February 3), Muller answered by stating that "…. sperm of males which are about a week old and have been copulating freely (as in Caspari's experiment) during that period have only about .07 or .08 % of lethal. Thus, the latter sperm, after 3 weeks, should contain something like .28 % of lethal."

On July 23, 1947 (American Philosophical Society 1947b), Stern writes Muller again stating that "I have mislaid your letter of some months ago (February 3, 1947, letter) in which you gave me some details of your own on the mutation rate under various physiological conditions. May I therefore ask you two questions and will you permit me to use your answers in a report which I am just preparing for the Manhattan Project? Obviously, full credit for it would be given. The questions are: (1) What is the spontaneous mutation rate in sperm derived from Canton-special males of from 3- to 6 days old? (2) What is the weekly increase in mutation rate of sperm from such males stored in females?"

On August 4, 1947 (Lilly Library 1947c), Muller responds "When sperm were stored in females, there was a weekly increase in the mutation frequency of about 0.07 %, on the average." On August 7, 1947 (American Philosophical Society 1947c), Stern cabled Muller asking him the temperature used and on August 8, 1947 (American Philosophical Society 1947d), Muller answered via cable indicating "25 °C." A subsequent undated letter, but most likely prior to September 9, 1947 (American Philosophical Society 1947e), Muller noted "A recalculation of my data gives the figure of 0.08 % instead of 0.07 % as the frequency of lethal accumulating in mature sperm per week." Since Uphoff and Stern (1947) did not include this correction in their report to the AEC it suggests that this undated letter was received after submittal of their report to the AEC.

The control value therefore used by Uphoff and Stern (1947) of 0.07 % for the estimated mutation rate of the sperm stored in the spermatheca was based on the earlier letter correspondence-supplied estimates of Muller (Lilly Library 1947b, c, February 3 and August 4) which Muller later clarified as being slightly in error.

The Caspari and Uphoff studies used Drosophila melanogaster fruit flies, breeding Canton-wild-type (S) males with Muller-5 females. Muller claimed (Lilly Library 1947c, August 4) that he never conducted mutation experiments with aged males of the Canton-wild-type stock. Muller stated that he had tested the aged sperm mutation frequency in "a number of different stocks (of Drosophila males) without finding any difference." The rate of increase on a weekly basis was said to be 0.07 % on average. This value of 0.07 % is believed to be prior to the correction to 0.08 %. This suggests that Muller did not observe significant inter-stock variation in mutation rates of the stored sperm.

Stern seems to have completed his Uphoff and Stern (1947) paper for the Manhattan Project during August, 1947. Stern knew that Uphoff's mean mutation frequency was 0.1682 % (0.1365–0.2097 %). This suggests a weekly mean increase in mutation rate of 0.0227 % (0.0122–0.0366 %), far lower than the 0.07 or 0.08 % mean weekly increase in Muller. When Stern wrote to Muller on September 9, 1947, he stated that for the Canton-special stock "…the weekly increase is considerably less than that found by you and others. It seems to be much more of the order of 0.03–0.05." This September 9,

1947, letter was written probably just after the submission of the Uphoff and Stern (1947) paper to the AEC, and definitely before the submission of the Caspari and Stern (1948) paper for publication by Genetics (i.e., November 25, 1947). Thus, the judgments of Uphoff and Stern that found that Uphoff's data were "uninterpretable" and that supported the reliability of the Caspari control data were made with the information provided by Muller during the summer of 1947. The apparent argument that Stern seems to be suggesting in his September 9, 1947, letter to Muller is that the Canton-wild-type stored sperm in the female may yield uniquely lower control mutation values. The argument is tenuous as the far higher weekly rate was consistently shown by multiple investigators, and with multiple Drosophila stocks, only being low in two Uphoff experiments. In fact, significant inter-strain differences on the frequency of dominant lethal mutations as induced by radiation were not reported in various Drosophila strains, including the Canton-special wild-type strain (Demerec and Fano 1944; Strömnaes 1951). This suggestion by Stern was not included in the Uphoff and Stern (1947) report.

This letter exchange between Stern and Muller fails to provide support for the later statements of Muller that Caspari's control group was unusually high. The Muller data and statements also do not provide support for the conclusion that the low Uphoff control data were in a normal range. None of this information was provided by Stern in his *Science* publication to permit the scientific community to better evaluate the Uphoff and Caspari control group data.

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