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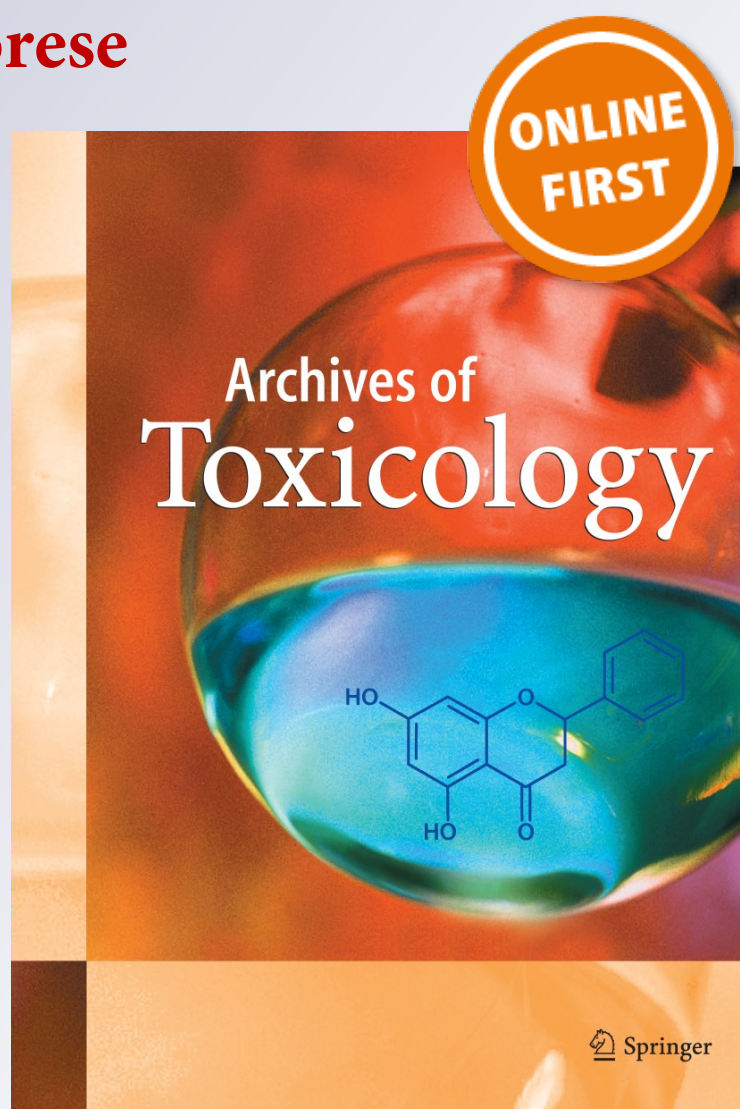
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Archives of Toxicology

ISSN 0340-5761

Arch Toxicol

DOI 10.1007/s00204-013-1177-3



 Springer

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Response to Letter of Ralph J Cicerone and Kevin Crowley regarding “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.” [DOI 10.1007/s00204-013-1105-6, Review Article]

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Received: 18 November 2013 / Accepted: 21 November 2013
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Dear Editor,

This letter addresses the concerns presented in the letter of President Cicerone concerning my 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” (Calabrese 2013). His summary of my historical conclusion of deliberate scientific misrepresentation by Curt Stern and Hermann J. Muller, which guided the decision of the NAS BEAR I Committee Genetics Panel to support the linear-no threshold model, is strikingly unrepresentative of the information and evidence presented in my article. President Cicerone provided an inaccurate account of my article, particularly when he accused its conclusions of not being justified by “actual supporting evidence.” He overlooks and fails to mention the significant amount of the evidence on which the conclusions of my article are based. The substantial amount of the evidence on which my article relied becomes clear when it is read and compared to his letter. Below I highlight some of the most significant elements of this evidence, which President Cicerone, inexplicably ignored. However, prior to my directly addressing the letter of President Cicerone I present a brief summary of my article and the process by which it occurred. This information is necessary to provide the proper context in which to evaluate the position articulated in President Cicerone’s letter.

My claim of deliberate scientific deceptions/misrepresentations by two renowned leaders of the radiation

genetics community, one a Nobel Prize winner, more than three decades after their deaths was made only after an exhaustive examination of the published literature, previously classified documents, and copious letters and other types of personal documents in the files of Curt Stern, Hermann J. Muller and other key people. The discovery of their scientific deceptions/misrepresentations occurred unexpectedly during research for an earlier paper entitled “Toxicology Rewrites its History and Rethinks the Future: Giving Equal Focus to Both Harmful and Beneficial Effects” (Calabrese 2011a, b, c). Prior to my submittal of this manuscript, I sent it to several people for a final set of informal evaluations. One reviewer’s comments, which suggested an extensive study of Muller and his role in the development of the linear-no-threshold (LNT) concept and its acceptance by regulatory agencies, prompted the present Muller–Stern–NAS investigation.

The first inkling of an “honesty” issue occurred after a detailed evaluation of Muller’s Nobel Prize Lecture of December 12, 1946 in which he vigorously denied even the possibility of a threshold response for radiation-induced genomic mutation, demanding a switch to a LNT risk assessment model (i.e., note Muller’s—“no escape from the conclusion that there is no threshold”—comment during his Nobel Prize Lecture). While his statements were not surprising, I linked them to data that had recently emerged at the University of Rochester. A newly completed chronic study on the effects of ionizing radiation on germ cell mutation in male fruit flies in August 1946 by Dr. Ernst Caspari, working under the direction of Stern, supported a threshold rather than a linearity dose response. The Caspari data were important since they were derived from the strongest low-dose-rate study to date.

The threshold findings were so unexpected and challenging that Stern, a strong proponent of the LNT, refused

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to accept the findings, claiming (without data to support his statement) that the control group was aberrantly high, leading to the false threshold conclusion. However, Caspari found strong literature support for his position, challenged the Stern position and eventually compelled Stern to reverse his stance and to accept or at least acknowledge the threshold conclusion.

Since Muller was a paid consultant to the Stern project, I wondered whether he had seen the Caspari findings prior to his Nobel Prize Lecture. I contacted individuals with expertise on the history of radiation genetics who had knowledge of Muller and Stern. However, no answer to my question was forthcoming. This led me to obtain considerable written correspondence between Stern and Muller and relevant colleagues. A series of letters between Stern and Muller starting in September of 1946 addressed the question. Stern initially told Muller that Caspari had finished his laboratory work, asked Muller if he would review the completed manuscript and Muller agreed. Stern sent Muller the manuscript on November 6 with Muller responding on November 12, indicating that the findings were important since they challenged the LNT in a highly significant manner and as such needed to be replicated as soon as possible. He noted that Caspari was a highly competent investigator, lending more credibility to the findings. He then stated that he would provide a detailed evaluation later. The letter on November 12 from Muller was the answer that I initially sought. Muller indeed had seen the findings of Caspari prior to his Nobel Prize Lecture, understood its importance and challenge to the LNT. Knowing this, Muller went to Stockholm and gave his Nobel Prize Lecture, inexplicably stating that there was no possibility that a threshold dose response could occur for ionizing radiation-induced genomic mutation. Yet, he had just seen copious data supporting this conclusion from the strongest study yet done on the question of chronic low-dose-rate effects, one on which he was a consultant, knew the research team, the facilities and had even supplied his own Muller-5 fruit flies.

I then questioned whether Muller might have changed his mind from the time of the letter on November 12 to Stern to when he gave the Lecture on December 12. However, his January 14, 1947, letter to Stern revealed this was not the case as he not only confirmed the original assessment but emphasized that he had no technical criticisms of the Caspari paper. Following this discovery of the misrepresentations of Muller, it raised two important questions: why would Muller risk his reputation and professional status, and why had this deception not been exposed for nearly seven decades?

Why Muller misled the Nobel Prize Lecture audience can only be speculated upon. It is known that Muller was passionate about his belief that X-rays would induce mutations and that most mutations were harmful. Even though he had an intuitive sense that such mutations could enhance

the risk of cancer, he was most concerned with the mutation load of the population. Soon after his discoveries of X-ray induced germ cell mutations, he had been on a mission to convince the medical community to be more responsible in their use of X-rays, especially those involving pregnant women and children. He also strongly advocated for the protection of those working with X-rays. Despite his activism, Muller was strikingly unsuccessful in convincing the medical establishment to adopt his views. He was blocked at each attempt. While Muller had rallied support from other radiation geneticists, it had not yet reached the tipping point to affect government risk assessment procedures or the medical community. Thus, when Caspari obtained data supporting a threshold response, it raised concerns among the radiation genetics community, prompting Milislav Demerec, the highly influential Cold Spring Harbor Chair of Genetics and future member of BEAR I committee, to ask Caspari what could be done to "save" the LNT single-hit theory. On the issue of mutation load, the radiation genetics community believed only they properly understood the problem and only they who could, in essence, save the world (i.e., human genome). It was within this context that Muller took to the podium in Stockholm on December 12, 1946, and made his landmark Nobel Prize Lecture. Muller's speech reflected a classic case of the ends (i.e., more conservative risk assessment procedures) justified his means (i.e., misrepresenting scientific understandings). As pointed out by his colleague and close friend, James Crow, it was not uncommon for Muller to exaggerate in order to win arguments, all to the frustration of his followers. Whatever the real explanation of "why," Muller's behavior at Stockholm revealed a clear case of deception.

Following these developments, more anomalies were uncovered. For example, although Muller could not offer any technical criticisms of the Caspari paper, the Stern directed—and the Muller approved—discussion of the Caspari manuscript was bizarre. The nearly six-page discussion was largely about why the threshold findings should not be accepted until it was determined why they differed from acute exposure which supported linearity as reported in an earlier Spencer study. Of note was that Caspari had incorporated a series of methodological and equipment changes improving upon the Spencer study. Secondly, the Spencer paper had a series of serious methodological flaws that threatened the reliability of its findings in the low-dose zone. Third, there were at least 25 significant experimental differences between the studies, making it impossible to directly compare them. Yet, Stern and Muller failed to see or report the limitations of the Spencer paper while setting up the Caspari manuscript as a type of straw man, preventing any serious consideration of the threshold findings. In fact, in his January 14, 1947, letter to Stern, Muller indicated that the Caspari manuscript could be published given

all the caveats (i.e., road blocks to its acceptance) they placed within the discussion. Caspari, therefore, would get the publication he needed, while the actions of Stern and Muller would blunt any potential impact of the threshold findings and preserve the LNT single-hit theory. I wondered what type of journal would even consider publishing a paper in which the authors demanded the reader not take seriously the data until it was resolved why its results differed from that of another paper when the resolution could not be realistically made. As it turns out, Stern “submitted” both the Spencer and Caspari papers (on which he was co-author) to the journal for which he was the editor (i.e., *Genetics*) on November 25, 1947, with publication occurring about one month later, in January of 1948, with no evidence of an independent peer-review for either paper. These acts of Stern and Muller were consistent with the goal of not only “saving the hit model” but also preventing Muller’s Nobel Lecture deception from being discovered.

Stern attempted to replicate the findings of Caspari, recruiting a new graduate student, Delta Uphoff. A significant problem arose in Uphoff’s research, obtaining aberrantly low control group values on repeated occasions. Muller’s copious control group data (which was consistent with the published literature) supported the validity of Caspari’s results while indicating that Uphoff’s were aberrant. In fact, in the discussion of their findings in a classified report for the Atomic Energy Commission, the aberrantly low control group values were surprisingly attributed by Stern and Uphoff to investigator bias, which resulted in the uninterpretable characterization of the findings.

When Stern finally did publish these findings as well as the summary results of Spencer and Caspari, it was as a single-page technical note in *Science*. In this note, Stern neglected to report that one year earlier, key findings of Uphoff’s research were considered as uninterpretable, due to investigator bias and that Muller’s confirmatory data supported Caspari but not Uphoff. Yet, Stern ignored these past assessments, revived the findings of Uphoff calling the control data normal while reversing his position on the acceptability of the Caspari data without justification for either decision...and without any apparent opposition. With the inclusion of the Uphoff and Spencer findings and the marginalization of the Caspari research, the data now would fit a straight line, supporting the LNT. Since no detailed methods and complementary data were provided in the one-page note, Stern promised to provide the missing information in a detailed subsequent paper. However, he failed to do so. A check of the citations and usage of these publications of Stern and colleagues revealed that the Uphoff and Stern paper in *Science* and the Spencer and Stern paper on acute effects in *Genetics* became widely cited and used to derive key understandings of the nature of the dose response in the low dose zone whereas the Caspari paper was not.

This observation gives insight and completion to the earlier comment of Demerek of “how can we save the hit model.” Stern had found a way to do it, deceptive that it was. Over the next several years, Muller would take the opportunity in his scientific writings to restate support for the Uphoff findings and to marginalize the Caspari work even though his own findings did just the opposite. Muller inexplicably restated the earlier mantra of Stern that Caspari’s control group was aberrantly high, falsely suggesting a threshold, knowing all the while that his own data were used to support the opposite conclusion. In later studies at the University of Indiana, his students would go on to support further the Caspari control group findings. Yet, Muller and Stern would fail to correct the record. Likewise, Caspari who once challenged Stern, now remained silent.

According to James Crow, by the early 1950s, the radiation genetics community had settled on the position that the LNT model needed to replace the threshold dose response for mutation. When BEAR I was created in 1955, I thought there would be considerable debate and discussion within the committee over the nature of the dose response in the low-dose zone, yet there was none, based on the transcripts. This issue had been decided before the panel met, and with the BEAR I Committee Genetics Panel stacked with supporters of Muller’s perspective, LNT became established. Muller and the radiation geneticist community used the vehicle of the NAS to finally achieve the long sought after goal to use LNT as the default model in risk assessment. In their committee publications and testifying before Congress, the BEAR I Genetics Panel members demonstrated their high reliance upon the Spencer and Uphoff papers, ignoring that of Caspari. Based on the prestige of the NAS and the failure of the NAS administration to properly evaluate the scientific basis of the BEAR I Genetics Panel report, their recommendations were quickly accepted, generalized to somatic cells, and applied to cancer risk for ionizing radiation and later for chemical carcinogens. This is where we are today. This historical summary is fully reported in a series of publications (Calabrese 2011a, b, c). Now consider how the letter of President Cicerone addressed the historical facts.

The letter of President Cicerone:

1. Omitted reference to the experimental replication efforts of Delta Uphoff (under Stern’s direction), their written acknowledgment of unacceptably low control group values and their recognition that certain key experimental results were “uninterpretable.” These were conclusions that they themselves provided to the Atomic Energy Commission in a formal manuscript that became classified.
2. Omitted the fact that Muller’s own findings, which were to be used to challenge the key mutagenicity threshold

data of Caspari, in the end unequivocally supported the reliability of the control values used in Caspari's study.

3. Failed to acknowledge that Muller was aware that his data not only supported both the Caspari control interpretation and the conclusion of a threshold response but also discredited the LNT conclusion of the Uphoff and Stern studies.
4. Failed to acknowledge that the Stern led discussion in the key Caspari threshold paper (Caspari and Stern 1948) had implored the reader not to accept their findings until they were reconciled with an earlier acute study (Spencer and Stern 1948) that seemed to support a LNT dose–response relationship. Stern wrote this knowing that the two studies differed methodologically in more than two-dozen important aspects and that these studies could never be directly compared. Also, the Caspari study was methodologically far superior to the earlier acute study (Spencer and Stern 1948), which had serious concerns regarding its scientific quality.
5. Failed to note that Muller argued in subsequently published material that the Caspari control group was aberrantly high, an argument that had already soundly dismissed using his own data (see #2). In fact, on this point, the entire set of correspondence between Stern and Muller and all subsequent data that further confirmed this conclusion were documented in my paper. Muller's deception on this critical point was as striking as it was easy to prove. The BEAR I Committee Genetics Panel never acknowledged nor challenged Muller on this point. President Cicerone's letter fails to address it as well.
6. Failed to note that Stern published the "uninterpretable" findings of Uphoff in *Science* without acknowledging that one year earlier, they decreed the same data to be "uninterpretable" due to strikingly low values in the control group (see #1), which was attributed to investigator bias in the discussion of their manuscript.
7. Failed to note that Stern reversed his position on the legitimacy of the Caspari study, leading to its rejection on the basis of high control group data, an already discredited conclusion.
8. Failed to acknowledge that Stern published only a one-page technical note on his five experiments, promising to provide a detailed paper at a later date containing all the data and methods. Yet, this promise was never kept.
9. Failed to acknowledge that the BEAR I Committee Genetics Panel never requested the detailed assessment.
10. Failed to acknowledge that the most reasonable and honest position that Muller could have displayed at the Nobel Prize Lecture was that there was uncertainty over the nature of the dose response in the low-dose zone and that more research was required. However, he strongly asserted that there was no longer any

basis to support even the possibility of a threshold model and that a switch to LNT was needed. He did this while knowing the results of the Caspari study, acknowledging privately in writing that the study seriously challenged the LNT, claiming he had no technical criticisms of the study, which was performed by a technically competent investigator, and calling for its replication. Thus, Muller behaved like a scientist in private but as an ideologue in public. There was no scientific basis for his statements.

11. President Cicerone claims that my article contained *ad hominem* remarks about Muller. These remarks claimed that Muller would attempt to win arguments via exaggeration and overstatement, frustrating his supporters. However, President Cicerone failed to state that this characterization of Muller's capacity to exaggerate (i.e., misrepresent) in order to win arguments was not mine but one offered by Muller's former student, colleague, close friend and BEAR Committee member, Professor James Crow (1995).

My article revealed that something seriously wrong occurred with the actions of Stern and Muller, leaders of the radiation genetics community. The failure of BEAR I Committee Genetics Panel to achieve its scientific mission of an objective and detailed appraisal of the scientific foundations of the dose response for mutation was also seriously wrong particularly given its societal importance. Yet, national leaders such as President Cicerone would prefer to protect the image of the NAS and the reputations of Stern and Muller rather than assessing objectively the foundations of the risk assessment scheme they created.

While President Cicerone claims that I have unfairly judged Stern and Muller, he is incorrect. The critical judgment emerges from their actions and words, as documented in open publications, now declassified publications and in publicly available private correspondence. The BEAR I Committee Genetics Panel did not study in detail the key papers upon which the decision on LNT was based, but relied upon the judgments of Stern and Muller. The NAS administration failed to properly vet the actions of this committee. The title of my article is appropriate and its content properly substantiated. It is there to be read by all.

Sincerely,

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