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Hermann Muller and his LNT scientific and policy leadership: Private communication reveals uncertainties

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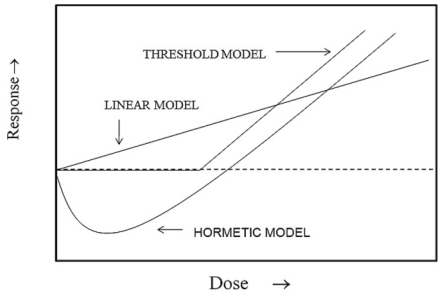
HIGHLIGHTS

- Hermann Muller helped create the LNT model.
- Muller was advocate LNT based cancer risk assessment.
- In private communication revealed considerable uncertainty about LNT.
- Muller created the concept of a precautionary principle in 1949.

GRAPHICAL ABSTRACT



Muller and Model Uncertainty

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ABSTRACT

The present paper highlights numerous publications of Hermann J. Muller with a focus on his opinions concerning the validity of the linear no-threshold dose response model for hereditary and cancer risk assessment. These comments reflect a very consistent and powerfully supporting position for the LNT model. However, newly discovered correspondence between Muller and Robley D. Evans reveals that Muller was highly uncertain about the supportive science, and therefore hid his real opinions, deliberately misleading the scientific community and governmental agencies. Of further historical value is that in the correspondence with Evans, Muller proposed what might be the first articulation of an environmentally based Precautionary Principle. These perspectives have remained unknown since Muller requested Evans to keep this letter private.

1. Introduction

Hermann J. Muller was awarded the 1946 Nobel Prize for Biology and Medicine for the production of mutations in *Drosophila*. He is also credited with the development of the concept of the linear no-threshold (LNT) dose response model for hereditary and cancer risk assessment.

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This was first clearly articulated in 1930 when Muller proposed the existence of the "Proportionality Rule" to describe the dose response nature of ionizing radiation induced mutation. The Proportionality Rule was soon morphed into the LNT single-hit model in 1935 in an article by Timofeeff-Ressovsky et al. (1935). Muller provided the paper with three critical features: ionizing radiation induced gene mutations, the assumption of no genetic damage repair component and an assumed linearity response down to a single ionization. In addition to providing the experimental foundations of the LNT concept and its theoretical foundations, Muller became a very outspoken and influential advocate for the adoption of the LNT concept in the areas of occupational health and in the application of this dose response concept in medicine. Muller would also become an influential member of the National Committee for Radiation Protection (NCRP) and the United States (US), National Academy of Sciences (NAS), Biological Effects of Atomic Radiation (BEAR) I Genetics Panel which recommended the adoption of LNT for hereditary risk assessment in 1956 (NAS/NRC, 1956), replacing the long-standing threshold dose response model (Calabrese, 2018, 2019, 2022). The LNT dose response model would become adopted by the US Environmental Protection Agency (EPA) after their creation in 1970. Given the controversies and debates associated with the LNT model and the unique leadership of Muller on this topic, it is of value to explore, as precisely as possible, what Muller believed as a scientist on the issue of LNT and whether his beliefs were consistent with the nature of his scientific and public leadership on LNT based heredity and cancer risk assessment issues.

2. The Muller-Evans letter revelation

Of considerable relevance to this issue is a letter that Muller sent to Robley D. Evans, a prestigious Massachusetts Institute of Technology (MIT) health physics professor on February 4, 1949 (Muller, 1949). Muller was responding to a manuscript that Evans had sent him and to over 50 other leaders in the area of radiation genetics and health physics. The manuscript was to be published in the journal *Science* on March 15, 1949 and set forth to challenge the LNT dose response model for ionizing radiation hereditary risk (Evans, 1949). Evans provided scientific arguments that supported the threshold dose response model while highlighting the limitations of the LNT model. The Evans paper gave particular attention to a recent paper published by Caspari and Stern (1948) which supported a threshold dose response in studies with *Drosophila*. It was the strongest and most relevant study to date on the topic of risks from chronic exposures to low doses of ionizing radiation. In fact, the study was part of the Manhattan Project genetic toxicology program at the University of Rochester under the direction of Stern, who had engaged Muller as a paid consultant. Muller had served in this role since 1943 and was a very active participant in these research activities (Calabrese, 2019). Thus, Muller was in possession of considerable insider information about the research staff, facilities, research questions and the strengths and limitations of the overall group activities.

It was well-known that Evans had sought out the advice of numerous high-level researchers, including those with strong support for the LNT model, with some being close colleagues of Muller. In general, the response that Evans received was strongly supportive of the threshold model, including those whose writings supported the LNT perspective, such as Curt Stern, James Neel, Donald Charles and others. However, the letter of Muller to Evans was anything but supportive. Muller used the letter to challenge the credentials and background of Evans to make legitimate comments on this topic which Muller felt was the distinct domain of the radiation genetics community and not in the realm of health physics. Muller also used his seven-page single-spaced letter to renew his disputes with other geneticists in such a bizarre manner that it had little ostensible relevance to the Evans paper. Of particular importance was that Muller challenged the scientific quality of the Caspari and Stern (1948) paper, claiming that Evans should remove the citation of this paper and that Evans needed to contact Curt Stern to learn of important methodological issues that compromised the paper. Muller then claimed that the Caspari and Stern research may have made a mistake in dosimetry, exposing their flies to 1/3 less radiation than reported in the paper. Toward the end of the letter to Evans, Muller reversed his aggressive approach and capped it off with an unexpected dose of personal, scientific and intellectual humility as shown in the quote:

Hermann Muller wrote to Robley D. Evans, MIT Health Physics professor on February 4, 1949: "Many of the quantities are only very roughly known even for Drosophila, and we are admittedly extrapolating too far in applying this to man…"

However, what came next was also quite surprising. Muller then asked Evans to keep the contents of his letter private, not to be shared with others. Given the attacks on multiple geneticists and the research of Caspari and his newly expressed humilities, there could have been multiple reasons why Muller would not have wanted Evans to have shared this letter with others. In fact, Evans honored the Muller request, only commenting that Muller's letter contained a combination of comments that reflected his prejudices and personal disputes. Nonetheless, the comment that "…we are admittedly extrapolating too far in applying this to man…" was a very revealing comment and one that contrasts with a long series of Muller's written or spoken statements (Table 1). If one were to have considered only Muller's public statements, one would see a very assertive and confident series of judgements and opinions, with these becoming further prominent after receiving the Nobel Prize in 1946.

3. What did Muller actually believe?

The question therefore needs to be asked as to who was the real Muller? What did he really believe on issues of human risk? Based on the letter to Evans, Muller was far from certain as to the quantitative nature of the dose response, even for *Drosophila*. His views on human responses and risks were extremely nebulous. Yet, the public Muller perspective was anything but uncertain and, apparently far overstated his case in the realm of public policy. According to his close colleague, Crow (1995), it was well known that Muller attempted to win arguments by exaggeration and overstatement. In fact, Crow emphasized that he found these actions of Muller to be exasperating as Muller would not uncommonly end up damaging his case by unnecessarily misrepresenting facts and circumstances, incorrectly believing that such actions would make him win his argument. So, what is the sympathetic Crow saying about Muller's honesty in the public domain?

Moreover, the quote of Muller does not end with the word "man"… but as follows: "but it is all we can do in our present state of ignorance and we must meanwhile remain on the safe side."

When seen in this broader perspective, it becomes clear that Muller's position was far less scientific and much more based on a public health philosophy. In fact, the statement of Muller would clearly qualify as being the basis of a Precautionary Principle. If Muller had made his letter public, it likely would have been personally embarrassing but it would have led to yet another first for Muller, that is, creator of the Precautionary Principle. Muller's written statement to Evans preceded by about a decade a type of Precautionary Principle arrangement that emerged from the NCRP on ionizing radiation induced cancer risks (Calabrese, 2021) which far preceded its broader international formulations in the early 1980s.

Credit authorship contribution statement

EJ Calabrese; created concept for the paper and wrote first draft.
PB Selby; edited and revised the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial

Table 1
Quotes of Muller concerning the LNT dose response model for ionizing radiation.

Reference	Quote
Muller, 1929. *The Scientific Monthly* (page 496)	"…there being no evidence of a minimal or 'threshold' dosage, we are forced to conclude that the minute amounts of natural radiation present almost everywhere in nature—some of terrestrial original…and of cosmic origin…all this natural radiation *must* be producing some mutations in the living things on the earth. ...It can, therefore scarcely be denied that in this factor we have found at least *one* of the natural causes of mutation and hence of evolution."
Muller, 1930. *The American Naturalist* (page 236)	"Since then Hanson, using radium, and Oliver in our laboratory using X-rays, have both found that the frequency of the mutations produced is exactly proportional to the energy of the dosage absorbed (as indicated by the amount of induced ionization). There is, then, no trace of a critical or threshold dosage beneath which the treatment is too dilute to work."
Muller, 1930. *The American Naturalist* (page 236, footnote 9)	"In Oliver's experiments it is especially evident that the proportionality rule holds strictly for the mutations produced—i.e. the remainder obtained by subtracting the frequency in the control from the frequencies the treated series is proportional to the dosage, even though control frequency varies significantly from one another in different experiments through unknown causes."
Muller, 1946. Nobel Prize Lecture	"In our more recent work with Raychaudhuri (1939, 1940) these principles have been extended to total doses as low as 400 *r*, and rates as low as 0.01 *r* per minute, with gamma rays. They leave, we believe, no escape from the conclusion that there is no threshold dose…"
Muller, 1947, Conference on Genetics and Public Health by The New York Academy of Medicine. Published in Bull NY Acad. Med vol 24, page 462.	"….the frequency of mutations induced will be proportional to the total dose of radiation received over an unlimited period of time."
Muller, 1950. *American Scientist* (page 126)	"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. *Physics and Medicine of the Upper Atmosphere* (page 317)	"A recent investigation by Stern and his co-workers, Spencer, Caspari, and Uphoff has extended the principle of proportionality of mutation frequency to dose down to doses of 50 and 25 r, and of less than 0.00l r per minute, with a time-intensity relation differing by over 400,000 times from that of our high-intensity dose." (Note that Muller made an error in that the 0.001 r per minute was 0.00165. This error then led to a second error with the over 400,000 value decreasing to 250,000 fold.)
	"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."
Muller, 1955. *Bulletin of the Atomic Scientists* (page 334)	"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."
	"In materials of varied kinds, but more especially with Drosophila, there is good evidence that over a considerable range of dose the frequency of point mutations is directly proportionate to dose."
Muller, 1957. *Congressional Testimony* (page 1066)	"…leukemia and some other malignancies, the induction of which may also be linearly dependent upon radiation dose…"
	"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…"
Muller, 1958. *Proceedings of 2nd UN International Conference on the Peaceful Uses of Atomic Radiation*, page 1	"This being the case, it is likely on theoretical grounds that the linear relation holds all the way down to zero dose."

interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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