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Manhattan Project genetic studies: Flawed research discredits LNT recommendations☆

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ABSTRACT

This paper reexamines the technical report (~ one page) of Uphoff and Stern (1949) in *Science* that was highly relied upon by the US National Academy of Sciences (NAS) Biological Effects of Atomic Radiation (BEAR) I Genetics Panel to support a linearity dose response for radiation risk assessment. The present paper demonstrates that research of Uphoff and Stern (1949) to evaluate whether total dose or dose rate best estimated radiation risks included two variables, thereby precluding the ability to accurately derive a reliable conclusion about this topic. Furthermore, the acute dose selected by Uphoff and Stern was given at a strikingly low dose rate that may have precluded the capacity to adequately test the total dose/dose rate hypothesis, even with a proper study design which also this research did not possess. The issue of total dose and dose rate was much later successfully addressed by Russell et al. (1958) using a murine model, yielding a dose-rate rather than a total dose conclusion. The failure to subject the experimental details of the Uphoff and Stern (1949) study to peer-review and publication in the open literature precluded a rigorous and necessary evaluation, profoundly and improperly impacting the adoption of the linear dose response model.

1. Introduction

During the Manhattan Project (1943–1946), research by the US Atomic Energy Commission (AEC) at the University of Rochester addressed the effects of ionizing radiation on mice and fruit flies (see Calabrese, 2011, 2019, 2020). The extensive murine-model research did not yield meaningful results due to failure to publish the findings in an appropriate time window, and the loss of essential data from the research record (Calabrese, 2019, 2022). However, a key publication based on that research was a technical note by Uphoff and Stern (1949), which assessed the effects of different dose rates of gamma radiation (from a radium source) on transgenerational phenotypic changes of the fruit fly. The one-page meta-experiment summary of Uphoff and Stern (1949) was instrumental in affecting the change from a threshold to a linear non-threshold (LNT) model for risk assessment of radiation-induced transgenerational mutations (NCRPM, 1960) and cancer (NCRPM, 1960) effects (Calabrese, 2019, 2022).

The research of Uphoff and Stern (1949) was designed to replicate the unexpected Manhattan Project-funded findings of Caspari and Stern (1948), which demonstrated that chronic exposures to gamma radiation with a total cumulative dose (i.e., accumulated over 21 days) of 50 rads failed to increase the occurrence of transgenerational phenotypic changes in the fruit fly. The Caspari and Stern (1948) chronic study comprised the second component of a two-part Manhattan Project investigation to assess whether total dose or dose rate was the best predictor of radiation-induced gene mutation. The first part of the larger study involved a series of acute exposures with the same fruit fly model (Spencer and Stern, 1948). The findings of Caspari and Stern (1948) suggested that the total dose hypothesis was incorrect and that low dose risk assessment is best represented by a threshold-yielding dose rate process. Given the potential major significance of the Caspari and Stern (1948) experiment, Stern obtained further funding to replicate the

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Caspari and Stern (1948) experiment based on recommendations of Hermann J. Muller to Stern (Muller, 1947).[1]

While the communications between Muller and Stern framed the subsequent Uphoff research to be a replication of the Caspari chronic exposure study, it was actually an examination of the issue of total dose versus dose rate, since the Caspari findings challenged the tentative conclusions of Ray-Chaudhuri (1939, 1944), and undermined the premise of the LNT model, thereby supporting the validity of a threshold model. Uphoff attempted what Spencer and Caspari sought to do, namely, to conduct both acute and chronic studies, and in this way, address – and seek to answer – the total dose/dose rate question. The initial experiment was a Spencer-like acute study, while follow up experiments were chronic (i.e., 50 and 100 rads total exposures). In contrast to Spencer's work that assessed multiple acute doses of X-rays, ranging up to massive dosing (i.e., 25–4000 rads), Uphoff assessed only a single acute dose of gamma radiation, at a comparatively small cumulative dose of 50 rads administered over 24 h. The acute dose study of Spencer (with dosing administered over several minutes) was compared to the same total dose of 50 rads delivered with a chronic exposure in the Caspari and Uphoff experiments, at a dose rate approximately 1/13,000 to 1/15,000 of that given in the acute study,[2] respectively.

2. The issue of study design

The chronic studies of Caspari and Uphoff and the acute experiment of Uphoff involved ionizing radiation exposure of sperm stored in the spermatheca (i.e., the sperm receptacle of the female) for three weeks. This storage period would also be utilized for exposure to gamma radiation in the chronic studies. The females were fed a diet that prevented egg development and fertilization for this three-week period; after which, the diet was changed to permit egg laying, fertilization, and subsequent testing to assess occurrence of transgenerational phenotypic mutational changes due to radiation exposure (Fig. 1).

The aging of retained sperm in the spermatheca had been associated with a marked increase in mutation rate over the three weeks by approximately 2.5-fold, as measured by transgenerational phenotypic changes (Calabrese, 2011, 2013). This increase in mutation rate was progressive, and increased over time in a constant manner.[3]

It is important to note that the Uphoff acute-exposure experiment represented a preconditioning study protocol. In preconditioning experiments, a stressor is administered prior to subsequent exposure to a second stressor/damaging agent. In the Uphoff experiment, the preconditioning "agent" was the sperm-aging mutation-enhancing process while sperm are stored in the spermatheca. Both the preconditioning aging process and the ionizing radiation in the acute study, which occurred at different times and are thus independent, may have increased transgenerational phenotypic mutational rates.

The acute exposure to gamma radiation was administered over a 24-h period, immediately following the three-week sperm storage period. Despite the use of lead shielding of the radium source, the control group received 0.6 rad from this treatment due to the physical proximity of the control and treatment group incubators (Uphoff and Stern, 1947). The radiation exposure to the control group during that 24-h period exceeded the background radiation rate by approximately 2000-fold. There was no evidence that this one-day radiation exposure of the control had any impact on the mutational findings.[4]

In the chronic radiation exposure study, Uphoff and Stern (1949) did not use a preconditioning exposure protocol. Rather, the protocol involved exposure to two continuous potentially mutational treatments: (1) the sperm aging storage process and (2) continuous/chronic gamma radiation exposure for the same three-week period. This indicates that the acute and the chronic exposure studies differed in two respects: First: acute (i.e., exposure over 24 h) versus chronic exposure (i.e., continuous over three weeks); and second: a preconditioning exposure prior to the acute (24 h) radiation dosing versus the radiation being continuously administered over the same three-week period when the sperm were aging. Since the timing of sperm aging with respect to the radiation exposure is different between the acute and the chronic studies, and because there is a different dose rate between the acute and chronic studies, the Uphoff and Stern (1949) research can be considered problematic, by virtue of having introduced two distinct and potentially interactive variables into the experimental protocol. That is, if a difference in mutational response was to be found between the chronic and acute groups, it would be important to query whether it was due to the difference in dose rate, or to the difference in the time of the radiation treatment in relationship to the sperm aging. Comparison might be further complicated by potential interaction(s) between the chronic irradiation and the mutational effects that occurred during sperm aging.

3. Discussion

3.1. Failure to publish findings

The data summarized in the Uphoff and Stern (1949) report of the Manhattan Project were never published in the peer-reviewed literature. Yet, these findings had a significant impact on the recommendation to abandon a threshold model in favor of a linear dose response model of radiation risk assessment for reproductive system and carcinogenic endpoints (Calabrese, 2019, 2022). While an appropriately detailed subsequent publication was promised (Uphoff and Stern, 1949), it was never provided/published. A technical summary report of the acute exposure work (6-page manuscript) was provided to the funding agency (Uphoff and Stern, 1947), but results of the two chronic studies by Uphoff and Stern were not. Consequently, findings of the Uphoff and Stern (1949) Manhattan Project research should not have received the level of scientific merit and standing that prompted the use of these results by the NAS BEAR I Genetics Panel (NAS/NRC, 1956) and by Lewis (1957) for radiation risk assessment. Furthermore, the Uphoff and Stern (1949) study design did not address or resolve whether radiation risk was best estimated via total dose or dose rate, given that their comparison used two variables concomitantly. These limitations of the Uphoff and Stern (1949) study have not been previously reported.

3.2. Control groups received substantial ionizing radiation

An important additional problem is that the "unexposed" control groups in the Uphoff and Stern studies did in fact receive substantial

[1] The Manhattan Project *Drosophila* radiation genetics study at the University of Rochester was intended to replicate the dissertation research of Ray--Chaudhuri (1939) from the University of Edinburgh that was conducted under the direction of Hermann J. Muller in 1938–1939. The research was affected by the start of World War II, ending the research prematurely before it was appropriately completed. Even though the research appeared to support the total dose hypothesis for estimating radiation-induced gene mutation risk, the dissertation had a number of important limitations that compelled Muller (1943, Muller letter to Stern) to suggest to Stern that he attempt to replicate the gene mutation (not the translocation) part of the Ray-Chaudhuri study, but to do so in a far more substantial manner.

[2] Note that Uphoff would conduct a second chronic study using a 100 rad total dose, following experimental concerns with her initial research (Calabrese, 2011, 2013). Since Uphoff did not conduct an acute study with 100 rads, this research was unable to answer the total dose vs dose rate question.

[3] This mutation rate of the aging sperm in the spermatheca was provided by Muller to Stern in private letters during the time of the Uphoff experiments at the University of Rochester (See Calabrese, 2013 for a summary of these letters and citations to the specific letters).

[4] The Uphoff and Stern control group values were reported to be inexplicably low for two of their three experiments, suggesting a potential problem in the execution of their experiments (see Calabrese, 2011, 2013; 2022).

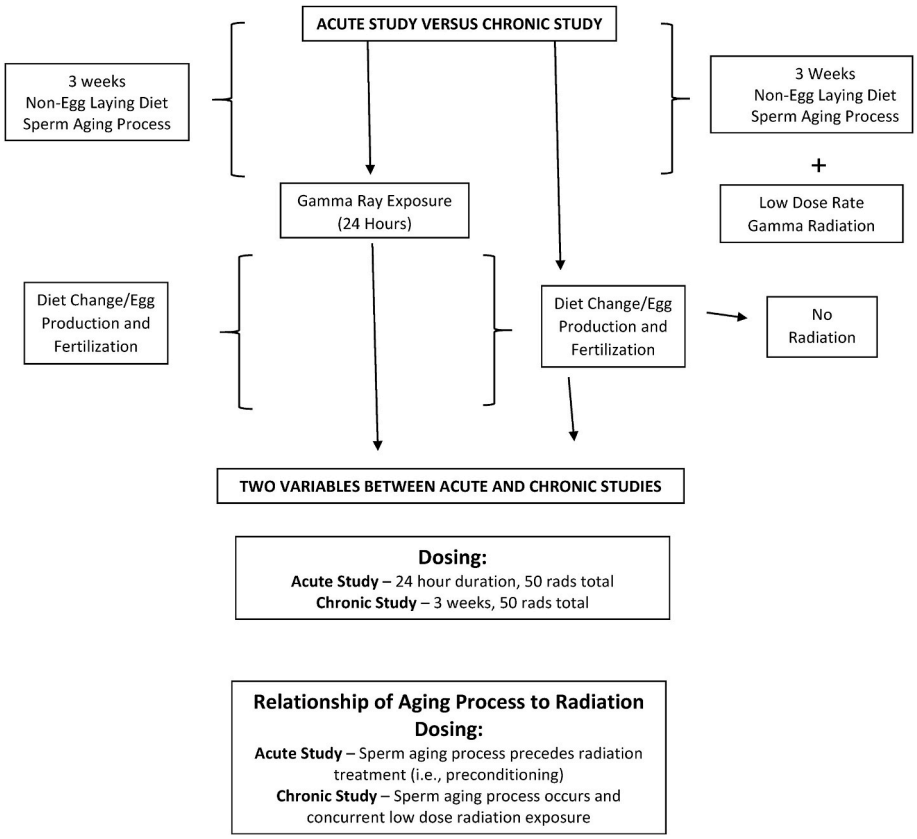

Fig. 1. Uphoff and Stern (1949) Flawed study design.

daily gamma radiation exposure, despite the use of lead shielding. The extent of the daily gamma radiation exposure to the respective control groups differed. The acute study control group received gamma radiation (0.6 rad) at approximately 2000-fold greater than the daily background rate for a single 24-h period. In the chronic studies, daily exposure of the control group was approximately 100–200-fold greater than daily background for the three weeks of the two chronic experiments. There was no evidence of control groups displaying elevated levels of supposedly spontaneous mutations in those experimental situations (i.e., spontaneous mutations, plus mutations induced by the irradiation of the "unexposed" control groups). Because the experiments discussed in this paper lacked concurrent non-irradiated controls, comparison can only be made to controls in other experiments. Uphoff and Stern (1949) never addressed this issue, and, as far as we know, it has not been discussed in the scientific literature to date. In light of these negative control group "exposure" findings of the three experiments, the possibility of a threshold response in this biological model cannot be excluded. Indeed, in two of these studies, the control rates were surprisingly/aberrantly low.

3.3. Consideration of flaws in study design

The question must be raised as to how this problem (viz. the study design flaw of having two variables) was not acknowledged by Stern, Muller, reviewers, and others - both at the time of the experiment and subsequently. Perhaps such an oversight was more likely because the investigators reported the experiments as separate entities, that is, as an acute experiment and a chronic experiment. Each of these experiments had a single variable and could be interpreted within that context. However, the central question tested was whether the best predictor of radiation-induced genetic damage was total dose or dose rate, and that question could only be addressed by comparison of the so-called acute and chronic studies. Moreover, the failure to acknowledge the presence of the two variables and their impact on the experimentation of the Manhattan Project might also be related, at least in part, to bias on behalf of Stern, Muller and other leaders of the radiation genetics community, who strongly supported the adoption of the LNT model to replace the threshold model in risk assessment. The extent of such bias is substantial and well documented (Calabrese, 2019, 2020), to the point where William Russell suppressed publishing the results of a major murine-model cancer study that contradicted the LNT perspective (see Calabrese and Selby, 2022). Similar methodological limitations (i.e., two variable issues) were also seen in the dissertation of Ray-Chaudhuri (1939). Other important limitations of the Ray-Chaudhuri (1939) research are detailed elsewhere (Calabrese, 2011, 2020).

3.4. Uphoff/stern study: Questionable acute dose selection to test hypothesis

When Russell et al. (1958) first investigated whether dose rate might be of consequence in the induction of gene mutations in mice, an experimental design was used that avoided methodological concerns such as the aforementioned issues in the fruit fly experiments. Long before his first dose-rate experiment, Russell had realized and emphasized that the germ cell stage (e.g., stem-cell spermatogonia in male mammals) was of overwhelming importance when investigating the induction of mutations. Russell demonstrated that mutation rates could be effectively determined in germ cells by using his specific-locus test (SLT). Because of the much greater importance of understanding potential hereditary risk from exposure of stem-cell spermatogonia, much greater emphasis was initially given to collecting offspring sired by irradiated males after the temporary sterile period caused by massive radiation exposures, or by waiting approximately seven weeks after exposure before allowing males to breed. Considerable emphasis was also placed upon ensuring that control groups received no more than background-level radiation.

Russell et al. (1958) administered 90 Roentgens (R) per minute in the acute study, and 0.009 R per minute in his first chronic experiment; this being a 10,000-fold difference in dose rate for the same total dose of 600 R. The acute and chronic exposures lasted approximately 7 min and 6 weeks, respectively. Using this comparison of acute and chronic dose rates, Russell introduced only one likely variable (i.e., dose rate), unlike the flawed design of the Uphoff and Stern studies. Russell acknowledged that his dose-rate experiment included an additional variable of radiation quality, given that the radiation in the acute experiment consisted of 250 kvp X-rays and, in the chronic experiment, the chronic dose was Cs^{137} gamma radiation. While Russell provided several reasons why he considered it unlikely that this difference in radiation quality explained the much lower mutation frequency found at the low dose rate, this issue was subsequently experimentally addressed and resolved. Russell et al. (1960) demonstrated a significant dose-rate effect using gamma radiation, with acute exposure being gamma radiation from Co^{60} delivered at 24 R/min. In subsequent work, Russell (1963) further demonstrated a significant dose-rate effect when using X-rays, with the dose rates being 90 R/min and 9 R/min.

Following the 1958 publication, Russell continued a series of experimental approaches using other dose rates (eventually as low as 0.0007 R/min), fission neutron exposures, and also involving different germ cell stages in both sexes in order to test, and then reject, other hypotheses that could possibly have caused a dose-rate effect (i.e.-instead of his accepted hypothesis that there was mutational or pre-mutational repair of DNA). The idea of repair, which was heretical when first proposed, was one of numerous principles related to mutation induction in mammals that could not have been predicted from the earlier work by Muller and others using *Drosophila* (Russell, 1973). Russell concluded that the mutation rate per R (Roentgen) in stem-cell spermatogonia was similar at 90 R/min and 1000 R/min. However, the mutation rate was significantly reduced from 90 R/min to 0.8 R/min. No further decrease in the induced mutation rate per R occurred as the dose rate decreased to 0.0007 R/min, the lowest dose rate tested, with total doses ranging from 37.5 to 861 R delivered at various dose rates (Russell and Kelly, 1982).

Russell speculated that there would be no further reduction in mutation rate per R at dose rates diminishing to background-level radiation. He also found no evidence of a dose-rate effect in spermatozoa, and concluded that there was repair of mutational or premutational damage in metabolically active cells (such as stem-cell spermatogonia and oocytes).

In hindsight when considering Russell's experiments, it is interesting and important to note that the Uphoff and Stern experiments, which were conducted about a decade before Russell's demonstration of a dose-rate effect, utilized an "acute" exposure of gamma-rays delivered over 24 h and a "chronic" exposure to the same dose over 3 weeks, which were equivalent to dose rates of 0.035 rad/min and 0.002 rad/min, respectively. Since rad and R are rather similar in magnitude, both of the dose rates used in the Uphoff and Stern experiments were within the range of 0.8 to 0.0007 R/min, for which the mutation frequency per R appears to be the same in stem-cell spermatogonia of mice. Thus, they could both be considered chronic exposures. Russell's data also suggest that no dose rate effect would be expected in spermatozoa of *Drosophila*. If such extrapolations from mice to *Drosophila* are indeed valid, then it appears that much of the importance related to risk estimation afforded to the technical note by Uphoff and Stern (1949) by the BEAR I committee was based, in fact, upon an unsatisfactorily reported experiment in *Drosophila* that had procedural flaws (i.e., in addition to the use of two variables as highlighted in this paper – Fig. 1. The Uphoff study also involved testing for a possible dose rate effect in a germ cell stage and at dose rates that were unlikely to show an effect even if one could occur in *Drosophila)*.

Soon after Russell's (1981) demonstration of a dose-rate effect in mouse spermatogonia, there were reports [Oster et al. (1959); Purdom and McSheehy (1961)] using female *Drosophila* of successful demonstration of similar dose-rate effects. Yet, it seems that those claims were apparently not convincing to Muller (1965) (as quoted in Russell, 1968), who presumably hoped that such an effect could not be found. To wit, Muller (1965) wrote about the final outcome of the search for a dose-rate effect in the fly as follows: "The repeated testing for it in *Drosophila* carried out by our group (Oster et al., 1959; Zimmering, Lee, and myself and unpublished) over the past four years has been agonizing in the pitfalls of its techniques. But the at-first positive-seeming and then vacillating data have been finally boiling down and resolving into a negative conclusion."

Russell (1968) noted that those tests covered a range of dose rates from 1 to 3000 rad/h, and that Purdom (1962) also tested for a dose-rate effect in *Drosophila* spermatogonia and indicated some effect at the lowest region of the range of tested dose rates; however, he noted that Purdom did not regard that single observation as conclusive. Russell (1981), when again discussing the attempt to demonstrate a dose-rate effect in *Drosophila*, wrote: "Extensive *Drosophila* results indicated that there would be no effect. A marked effect was found in the mouse, however, in spermatogonia, but not in spermatozoa [reference provided in that paper]. Because the *Drosophila* data had come from spermatozoa, it was widely believed that *Drosophila* spermatogonia might show a dose-rate effect like that in the mouse. H.J. Muller immediately started testing this possibility for sex-linked mutations in *Drosophila*. For various technical reasons, he chose oogonia rather than spermatogonia. He ended this work very disappointed that, despite intensive investigation, he was not able to show to his own satisfaction a clear-cut effect of dose rate, and he concluded that mice and flies are simply different. He generously congratulated us on finding a basic principle important for risk estimation that had been missed in *Drosophila* studies." (Russell, 1981). Russell went on to describe an Abrahamson and Meyer (1976) paper that re-analyzed Muller's data and claimed that Muller might have made an error and thereby missed seeing a small dose-rate effect. Russell noted that if they were correct, that would mean that it took 18 years for the *Drosophila* results to be "brought in line with those in the mouse." He wondered, had Muller still been alive, if he would have agreed with the re-analysis, and even if he did, Russell wrote that it would have been better to have a dose-rate study in *Drosophila* using specific-locus mutations.

Calabrese et al. (2022) recently presented numerous arguments for why the existence of repair at low dose rates should be viewed from an evolutionary perspective. It is fascinating that Muller (1965), who was probably the most forceful proponent of efforts to replace the threshold model with the LNT model, concluded that mice and flies were probably different regarding a dose-rate effect and invoked an evolutionary basis for the difference between mice and flies. As characterized by Russell (1968), Muller believed that, "… if mammals were as much affected by the chronic radiation of nature as by the same amount of acute radiation, they might have enough genetic damage induced in their germ cells, and also in their somatic cells, to provide an appreciable selective advantage to those lines that had a protective mechanism against the chronic radiation, whereas in flies such an influence would be so much weaker as probably to be below the threshold for natural selection."

Thus, this highly influential geneticist appears to have provided clear suggestions that evolution might lead to effective mechanisms to repair DNA in germ cells and somatic cells, and also to have suggested that thresholds might be important regarding such effects. Russell (1965) considered the dose-rate effect to have been confirmed independently in mice by Phillips (1961), in silkworms by Tazima et al. (1961), and in the wasp, *Dahlbominus*, by Baldwin (1965).

3.5. The issue of two variables

The stressing of a biological system within an appropriate time frame prior to a more severe stress can upregulate adaptive mechanisms capable of reducing damage from subsequent stress. This phenomenon was designated "preconditioning" by Murry et al. (1986), although it

was first reported nearly a century ago in studies of the effects of radiation on plant growth (Ancel and Lalemand, 1928). A comprehensive assessment of preconditioning (often referred to as adaptive response) by Calabrese (2016a,b) indicates that it is a manifestation of hormesis, with responses typically following the biphasic dose response (with unique quantitative features for response amplitude and width of stimulation). This has relevance for the Uphoff and Stern (1949) paper, given that preconditioning stress can either protect against the subsequent stress exposure or enhance it, depending upon the magnitude of the preconditioning exposure. This would have been the case in the acute experiment of Uphoff and Stern (1949). In contrast, a continuous co-exposure to the sperm-aging stress and the ionizing radiation occurred in the Uphoff and Stern chronic experiment. Since Uphoff and Stern did not study this issue, or cite literature addressing the topic, it appears that the second variable was introduced without controversy or additional consideration. Nevertheless, the introduction of this second variable into the chronic study represented a flaw in the study design, since they were trying to assess total dose versus dose rate effects.

As the preconditioning concept preceded the Uphoff and Stern (1949) report by two decades, and had its origin in the radiation literature (Ancel and Lalemand, 1928), the preconditioning concept had the potential to have been identified by leaders of the genetics community such as Stern, Muller, Spencer and others on the Manhattan Project team. In fact, by 1950, Pape strikingly linked radiation preconditioning to the hormetic biphasic dose response concept. Even if it was unknown to Stern, the experimental design should have been such as to preclude the introduction of two variables, unless extremely well justified, and that certainly was not the case in the Uphoff and Stern report (1949).

4. Conclusion

The question of whether total dose or dose rate alone determined the extent of radiation-induced mutation was a central research question of the Manhattan Project. The data of Uphoff and Stern (1949) were used to provide substantial support for the total dose hypothesis, leading to the adoption of the linear dose response model for radiation risk assessment, and the rejection of the threshold model by the NAS BEAR I Genetics Panel. The present assessment shows that the Uphoff and Stern (1949) research was incapable of addressing this question due to methodological limitations that have been unrecognized to date. Furthermore, in hindsight, and especially in view of William Russell's elucidation of numerous biological factors in the murine model that are of significant importance to mutational responses, and which could not have been imagined based solely upon the prior extensive work in *Drosophila*, the entire methodological approach used in the Updoff and Stern experiments appears to be almost irrelevant to the dose-rate question. Soon after Russell's discovery of the dose rate effect, and before many of his important follow-up experiments were conducted, the LNT model was adopted by the US government (Federal Radiation Council, 1962) in 1962 for risk assessment, as based largely upon the advice of radiation geneticists, many of whom were members of the BEAR I Genetics Panel (Calabrese, 2020). The present paper seeks to contribute to the growing body of information on the reconstruction of the historical foundations of cancer risk assessment, and how the models and methods used were critical to the adoption of certain standards and practices. It is our hope that by bringing these findings – and the events that were contributory to their use – to light, current and future studies will be more rigorous and adept in conduct and dissemination.

Author statement

EJC, Conceptualization, literature review, writing – original draft preparation; EA and JG, reviewing and editing; PBS writing, reviewing and editing.

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Declaration of competing interest

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

Data availability

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

References

Abrahamson, S., Meyer, H.U., 1976. Quadratic analysis for induction of recessive lethal mutations in Drosophila oogonia by X irradiation. In: Biological and Environmental Effects of Low-Level Radiation, vol. 1. International Atomic Energy Agency, Vienna, pp. 9–18.

Ancel, P., Lalemand, S., 1928. Sur la protection contre l'action des rayons X par une irradiation prealable (radiophylaxie). CR Soc Biol 99, 1588–1590.

Baldwin, W.F., 1965. Visible mutation frequencies in *Dahlbominus* oogonia produced by acute X-rays and chronic γ-radiation. Mutat. Res. 2, 55–59.

Calabrese, E.J., 2011. Key studies to support cancer risk assessment questioned. Environ. Mol. Mutagen. 52 (8), 595–606.

Calabrese, E.J., 2013. 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. Arch. Toxicol. 87, 2063–2081.

Calabrese, E.J., 2016a. Preconditioning is hormesis. Part I: documentation, dose-response features and mechanistic foundations. Pharm. Res. (N. Y.) 110, 242–264. https://doi.org/10.1016/j.phrs.2015.12.021.

Calabrese, E.J., 2016b. Preconditioning is hormesis. Part II: how the conditioning dose mediates protection: dose optimization within temporal and mechanistic frameworks. Pharm. Res. (N. Y.) 110, 265–275. https://doi.org/10.1016/j.phrs.2015.12.020.

Calabrese, E.J., 2019. The linear no-threshold (LNT) dose response model: a comprehensive assessment of its historical and scientific foundation. Chem-Biol Inter 301, 6–25.

Calabrese, E.J., 2020. Ethical failures: the problematic history of cancer risk assessment. Environ. Res. 193, 110582T.

Calabrese, E.J., 2022. Linear non-threshold (LNT) fails numerous toxicological stress tests: implications for continued policy use. Chem-Biol Inter 365, 110064.

Calabrese, E.J., Selby, P., 2022. Cover up and cancer risk assessment: prominent US scientists suppressed evidence to promote adoption of LNT. Environ. Res. 210, 112973.

Calabrese, E.J., Shamoun, D.Y., Agathokleous, E., 2022. Dose response and risk assessment: evolutionary foundations. Environ. Pol. 309, 119787.

Caspari, E., Stern, C., 1948. The influence of chronic irradiation with gamma-rays at low dosage on the mutation rate of Drosophila melanogaster. Genetics 33, 7595.

Federal Radiation Council, 1962. Health implications of fallout from nuclear weapons testing through 1961. Report 3, 1–10.

Lewis, E.B., 1957. Leukemia and ionizing radiation. Science 125, 965–972.

Muller, H.J., 1943. Letter to Stern. Muller Mss. Lilly Library, Manuscript Department, Indiana University, Bloomington. IN. October 12.

Muller, H.J., 1947. Letter to Stern. American Philosophical Society, vol. 14. Stern Papers, Muller File, January, Philadelphia, PA.

Muller, H.J., 1965. In: Geerts, S.J. (Ed.), *Genetics Today (Proc. 11th Intern. Cong. Genet.*, the Hague, Sept. 1963), vol. 2. Pergamon, Oxford, p. 265.

Murry, C.E., Jennings, R.B., Reimer, K.A., 1986. Preconditioning with ischemia-a delay of lethal cell injury in ischemic myocardium? Circulation 75 (5), 1124–1135. https://doi.org/10.1161/01.cir.74.5.1124.

National Academy of Sciences (NAS)/National Research Council (NRC), 1956. The Biological Effects of Atomic Radiation: A Report to the Public. NAS/NRC, Washington, DC.

NCRPM (National Committee on Radiation Protection and Measurement), 1960. Somatic radiation dose for the general population. Report of the ad hoc committee of the NCRPM, may 6. Science 131 (3399), 482–486.

Oster, I.I., Zimmering, S., Muller, H.J., 1959. Evidence of the lower mutagenicity of chronic than intense radiation in Drosophila gonia. Science 130, 1423.

Pape, R., 1950. Histological Findings after Very Small Doses of Irradiation. 6th Int Congr Radiol, London, pp. 162–163.
Phillips, R.J.S., 1961. A comparison of mutation induced by acute X and chronic gamma irradiation in mice. Br. J. Radiol. 34, 261–264.
Purdom, C.E., 1962. In: Sobels, F.H. (Ed.), Repair from Genetic Radiation Damage (Symp., Leiden, Aug. 1962. Pergamon, Oxford, p. 219.
Purdom, C.E., McSheehy, T.W., 1961. Radiation intensity and the induction of mutation in Drosophila. Int. J. Radiat. Biol. 3, 579–586.
Ray-Chaudhuri, S.P., 1939. The validity of the Bunsen-Roscoe law in the production of mutations by radiation of extremely low intensity. In: Edinburgh, Scotland, Punnett, R.D. (Eds.), Proc. 7th Intern Genetics Congress. Cambridge at the University Press, UK, p. 246. Published 1941. Abstract Number 249 August 23-30, 1939.
Ray-Chaudhuri, S.P., 1944. The validity of the Bunsen-Roscoe law in the production of mutations by radiation of extremely low intensity. Proc R Soc Edin 62, 66–72.
Russell, W.L., 1963. The effect of radiation dose rate and fractionation on mutation in mice. In: Sobels, F. (Ed.), Repair from Genetic Radiation. Pergamon Press, Oxford, pp. 205–217, 231-235.
Russell, W.L., 1965. The nature of the dose-rate effect of radiation on mutation in mice. Suppl, Jap J Genet 40, 128–140.
Russell, W.L., 1968. Repair mechanisms in radiation mutation induction in the mouse. Proceedings of the 20th Brookhaven Symposia in Biology, "Recovery and Repair Mechanisms in Radiobiology 179–189.
Russell, W.L., 1973. Mutagenesis in the mouse and its application to the estimation of the genetic hazards of radiation. In: Duplan, J.F., Chapiro, A. (Eds.), Advances in Radiation Research, Biology and Medicine. Gordon and Breach Science Publishers, New York, pp. 323–334.
Russell, W.L., 1981. Problems and solutions in the estimation of genetic risks from radiation and chemicals. In: Berg, G.G., Maillie, H.D. (Eds.), Measurement of Risks. Plenum Press, New York, pp. 361–380.
Russell, W.L., Kelly, E.M., 1982. Mutation frequencies in male mice and the estimation of genetic hazards of radiation in men. Proc. Natl. Acad. Sci. U.S.A. 79, 542–544.
Russell, W.L., Russell, L.B., Kelly, E.M., 1958. Radiation dose rate and mutation frequency. Science 128 (3338), 1546–1550.
Russell, W.L., Russell, L.B., Kelly, E.M., 1960. Dependence of mutation rate on radiation intensity. Symposium on "immediate and low level effects of ionizing radiation. Venice 1959 Intern J Rad Biol, Supplement 311–320.
Spencer, W.P., Stern, C., 1948. Experiments to test the validity of the linear R-dose mutation frequency relation in drosophila at low dosage. Genetics 33, 43–74.
Tazima, Y., Kondo, S., Sado, T., 1961. Two types of dose-rate dependence of radiation-induced mutation rates in spermatogonia and oogonia of the silkworm. Genetics 46, 1335–1345.
Uphoff, D., Stern, C., 1947. Influence of 24-hour Gamma Ray Irradiation at Low Dosage on the Mutation Rate in Drosophila, MDDC-1492. US Atomic Energy Commission. Hathi Trust Digital Library, pp. 1–6.
Uphoff, D.E., Stern, C., 1949. The genetic effects of low intensity irradiation. Science 109, 609–610.