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REVIEW ARTICLE

Background radiation and cancer risks: A major intellectual confrontation within the domain of radiation genetics with multiple converging biological disciplines

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ABSTRACT

This paper assesses the judgments of leading radiation geneticists and cancer risk assessment scientists from the mid-1950s to mid-1970s that background radiation has a significant effect on human genetic disease and cancer incidence. This assumption was adopted by the National Academy of Sciences (NAS) Biological Effects of Atomic Radiation (BEAR) I Genetics Panel for genetic diseases and subsequently applied to cancer risk assessment by other leading individuals/advisory groups (e.g., International Commission on Radiation Protection-ICRP). These recommendations assumed that a sizeable proportion of human mutations originated from background radiation due to cumulative exposure over prolonged reproductive periods and the linear nature of the dose-response. This paper shows that the assumption that background radiation is a significant cause of spontaneous mutation, genetic diseases, and cancer incidence is not supported by experimental and epidemiological findings, and discredits erroneous risk assessments that improperly influenced the recommendations of national and international advisory committees, risk assessment policies, and beliefs worldwide.

KEYWORDS

Cancer risk assessment; chemical risk assessment; dose-response; mutation; radiation; linear dose-response

Introduction

In 1928, Olson and Lewis claimed that background radiation-induced mutation was the mechanism of evolution. This was based largely on the discovery of X-ray-induced phenotypic changes in the offspring of male fruit flies that Muller (1927) claimed were gene mutations. However, since Muller (1927) did not provide data in this publication, Olson and Lewis (1928) relied on the research of Goodspeed and Olson (1928) with X-ray-induced plant mutations. While the proposal of Olson and Lewis (1928) was broadly supported (Babcock and Collins 1929; Muller 1929), Muller and Mott-Smith (1930) subsequently challenged their evolution-mechanism interpretation. Muller and Mott-Smith (1930) reported that using a linear/proportionality model and applying it to the Muller (1927) mutation data, accounted for only about 1/1300th of the mutations reported in the control group.[1] This strikingly low estimate discredited the proposal of Olson and Lewis (1928) removing background radiation as the, or even a significant factor affecting evolution. The remaining > 99.99% of the evolution-driving mutation load in the control group originated from other unknown causes. Even though the Muller and Mott-Smith (1930) report effectively ended the debate over background radiation as the principal cause of biological evolution, Muller (1955) nonetheless later proposed that background radiation played a significant role in the occurrence of genetic defects and cancer in humans. While this issue was slow to materialize, discussions on this topic acquired a notable focus in the mid-1950s (Huxley 1955; Muller 1955; Spiers and Haldane 1956; Haldane 1956a; Glass 1957), being largely driven by emerging human health concerns due to nuclear fallout in the United States (U.S.) since the start of above-ground nuclear explosion testing in the western state of Nevada in 1951 (Calabrese 2019).[2] The issue of background radiation is not just one of historical concern but remains a central core of contemporary debate on the LNT concept and its applications to hereditary and cancer risk assessment. This contemporary debate

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Table 1. Key historical publications affecting background radiation risk assessment.

Date	Historical Significance
1928	Goodspeed and Olson proposed that background radiation is the mechanism of evolution.
1930	Muller and Mott-Smith discredit the Goodspeed and Olson proposal; background radiation only accounted for 1/1300th of the fruit fly control group mutation rate.
1955-1956	Muller and others attempt to restore significance of background radiation for human hereditary disease and cancer due to longer reproductive period and lifespan.
1958-1959	Russell establishes dose rate and repair of radiation induced genetic damage.
1956-1980	Harman proposes that metabolic generation of free-radicals is the mechanistic driver of evolution.

on background radiation and public health risks is assessed as part of this paper.

Background radiation risks reconsidered with application to longer-lived species such as humans

Section concept overview: Background radiation vs. endogenous metabolism as the principal mechanistic driver of evolution

In the 1950s, leading radiation geneticists revitalized the hypothesis that background radiation had a significant impact on human hereditary disease and cancer risks due to its prolonged reproductive period and lifespan. This highly influential idea would become discredited by Harman (1956, 1962, 1980) and others who discovered that endogenous metabolism generates vastly more oxy-radicals/cells/day than background radiation (Table 1).

Background radiation risks evaluated

The intellectual revival of the public health concerns regarding background radiation was rooted in the fact that humans have a profoundly longer reproductive life and lifespan than the fruit fly and that genetic/-mutational damage from background radiation would continue to accumulate in stem-cell spermatogonia over multiple decades. Further, by the 1950s concerns with background radiation expanded from those of birth defects, which dominated the perspectives of the radiation geneticists in the 1930 to 1950 period, to mutation-induced leukemias and cancers following the atomic bomb explosions in Japan in 1945.

In the mid-1950s, Muller (1955) estimated that background radiation may have accounted for roughly 8–16% of the total new spontaneous mutations that occur in human offspring. This background radiation rate estimation was published by Muller (1955) just as the US NAS BEAR I Genetics Panel (Panel) was initiated (i.e., November 1955). In addition to the derivation of these estimates, Muller (1956a) also provided a more rigorous attempt to estimate the contribution of background radiation to the spontaneous mutation rate in an unpublished document provided to the BEAR I Genetics Panel. Muller (1955; Muller 1956a) acknowledged that these estimates involved incomplete information and the use of multiple assumptions, making the estimates uncertain.

The Panel estimates were dependent on Muller's fruit fly studies and on mouse data from William L. Russell (Oak Ridge National Laboratory) using the specific locus test that determined background mutation frequencies at seven genes, estimates of the total number of genes in the mouse model, the gene mutation frequency per rad, and the assumption of a linear dose-response for ionizing radiation[3].

There are several concerns with the Muller fruit fly and human analyses. Muller's work involved the assumption that the observed genetic effects were gene mutations, that the dose-response was linear to a single ionization, and that the findings with the fruit fly were quantitatively relatable to humans, as described below:

a. Lack of Gene Mutation: Muller (1927) assumed that the very high dose rates of X-rays used induced gene mutation in fruit flies. However, this perspective was progressively challenged in the 1930s, and by the mid-1950s Muller (1956b) acknowledged that he had induced principally moderate to massive gene deletions rather than mutations, a conclusion supported by modern analytic methods (Calabrese 2019).
b. That Muller principally induced gene deletions challenged the validity of the linear non-threshold (LNT) single-hit model that was based upon point mutations and on the assumption that repair did not occur (Calabrese et al. 2022).
c. Glass (1957) and some of his colleagues (Muller 1954a; 1954b; Haldane 1955; 1956a; 1956b) asserted that the impact of background radiation on human gene mutation would be much higher than in the shorter-lived fruit flies, based on the profoundly longer duration of the human reproductive period, ranging from days in the fruit fly to several decades in humans. Accordingly, the human genome was predicted to sustain about

1,000-fold greater genetic damage than the fruit fly (Huxley 1955; Medical Research Council (MRC) 1956; Haldane 1956a; Glass 1957) due to its prolonged exposure to background radiation. Glass (1957) stated that "for longer-lived animals, a greater [mutation] fraction may well be caused by the background since the over-all mutation rate in different species holds fairly constant (within about one order of magnitude) (see Lynch 2007, 2008, 2010a, 2010b), although the exposure to background radiation increases enormously with length of life. If the low-level radiation of the background causes a proportionate increase of mutation, then in a species that lives a thousand times as long as *Drosophila* and whose gonads are equally exposed, "all spontaneous mutation would be caused by the background." This lifespan argument would come to dominate the thinking of leading radiation geneticists who were attempting to translate the perceived genetic risks in fruit flies and make them quantitatively relevant to humans (Muller 1954b; Haldane 1955; Haldane 1956a; Haldane 1956b; Medical Research Council (MRC) 1956; Muller 1956a).

d. Multiple lines of interdisciplinary evidence would soon undermine this radiation geneticist perspective. From the field of chemical toxicology came the report of Dannenberg (1958) that claimed that most human cancers resulted from endogenous steroid metabolites, a hypothesis based on findings that endogenous steroids are structurally very similar to the then well-known carcinogenic polynuclear aromatic hydrocarbons. This was the first widely recognized direct challenge to the radiation mantra that background radiation was the most likely cause of spontaneous mutation/-cancer. This perspective was substantially expanded over the next two decades by Soloway and LeQuesne (1980) who added numerous additional carcinogenic endogenous agents to the Dannenberg (1958) list, while also establishing dose-response relationships and underlying mechanistic foundations.

Preceding the 1958 paper of Dannenberg was the 1956 often-cited and groundbreaking hypothesis of Denham Harman (1956) at the University of California at Berkeley (later moving to the University of Nebraska) that aging was principally due to the endogenous generation of free radicals by normal metabolism. Harman (1956) initially qualitatively stated that metabolism added greatly to the oxy-free radicals produced by background radiation. Within a few years, quantitative estimates would show that background radiation was not a significant quantitative contributor of oxy-free radicals, with metabolism being the overwhelming contributor. By 1962, Harman advanced the hypothesis that endogenous metabolism was the principal cause of the massive daily load of oxy-free radicals that not only drives aging and cancer processes but is the underlying mechanism of biological evolution. The arguments of Harman (1956, 1962, 1980) also undercut the cumulative effects view of background radiation since the endogenous oxy-radiations were similarly "cumulative", with this constant presence over time.

At approximately the same time, there was substantial research on biological allometry (Adolph 1949; Pinkel 1958), relating body weight and surface area to numerous other parameters including metabolism, oxygen utilization, and free radical generation. Of particular importance was the observation that shorter-lived mammals, such as mice and rats, displayed considerably greater respiration rates, heart rates, and metabolism than longer-lived mammals, including humans. These findings inspired research in the area of DNA damage and repair which then showed that the quantities of mutagenic metabolites produced and excreted were much higher in the shorter-lived mouse and rat models per unit of time than the human. The allometric framework therefore overwhelmed and integratively corrected for the duration hypothesis of Glass, Huxley, and others in the radiation genetic community.

The perspective of Harman (1980) that endogenous metabolism was the overwhelming cause of background mutation was extended by leaders in the radiation biological community such as Totter (1980), Setlow (1988), Billen (1990), Pollycove and Feinendegen (2003), Robinson et al. (2018) and Yousefzadeh et al. (2021). These researchers were particularly focused on placing the perspectives of Muller and his colleagues within a more refined quantitative context, in light of five decades of research.

Totter (1980) noted that daily background radiation generates about 1/10 billionth of the oxygen radicals per gram of tissue compared to that generated by daily ingestion of food, making the impact of background radiation practically imperceptible (Totter 1980). This view is strongly supported by the spate of negative epidemiological studies that have assessed background radiation and its public health impacts (see Wakeford et al. (2009); Ricci and Tharmalingam (2019); for a summary).

Not only was the proposal of Harman transformative, but it also had the potential to discredit the nearly three-decade-old LNT hypothesis of Muller. Thus, by the early 1960s, there was a major intellectual confrontation within the domain of radiation genetics with multiple converging biological disciplines (i.e., chemical toxicology, free radical biology, DNA repair, biological allometry, and cancer epidemiology) over the major mechanisms of evolution, the causes of aging and cancer, and the capacity to account for the increase in cancer to the 6^{th}–7^{th} power of age based on epidemiological studies (Pollycove and Feinendegen 2003).

It is now recognized that endogenous/metabolic factors cause >99.99% of control group mutations, with background radiation having no readily quantifiable impact (Lutz 1990; Smith 1992; Marnett and Burcham 1993; Gupta and Spencer-Beach 1996; Gupta and Lutz 1999; Williams and Jeffrey 2000; Jackson and Loeb 2001; De Bont and van Larebeke 2004; Tubbs and Nussenzweig 2017; Vijg 2021; Yousefzadeh et al. 2021). In a detailed assessment of endogenous mutations and their repair, Pollycove and Feinendegen (2003) reported the quantity of DNA damage due to endogenous reactive oxygen species (ROS) when adjusted for repair half-life. The probability of a single DNA nucleotide being endogenously damaged/day/cell is 10^6 per total number of nucleotides (i.e., 6 x 10^9) or about 1.5 damaged nucleotides/10,000 nucleotides. The daily production of endogenous DNA alterations was estimated by Pollycove and Feinendegen (2003) to exceed that produced by low linear energy transfer (LET) background radiation by about 200,000,000-fold/cell/day. They concluded that this massive ratio indicates that the system that regulates DNA damage repair and sustains cellular integrity evolved in response to endogenous damage instead of background radiation due to the massive differential in damage production. Due to an array of repair-related processes, the $\sim 10^6$ genetic damage events/cell/day get repaired except for about one/cell/day, leading to about 30,000 such mutational residues/cell by the age of 80 years. Mutations from background radiation and endogenous metabolism are rapidly repaired, including single-strand breaks (SSBs) and double-strand breaks (DSBs).

At the time of the NAS BEAR I Genetics Panel (1956) meetings (November 1955-June 1956), the amount of radiation needed to induce a mutation rate equal to the spontaneous rate (i.e., the doubling dose [DD] concept) was estimated to range from 5-150 R depending on a variety of assumptions. According to Crow (1995), a member of that BEAR I Genetic Panel, a DD in the vicinity of 4-5 R implied that all mutations were due to background radiation, a view that was advocated by Huxley (1955), Haldane (1956a) and others. The BEAR I Genetics Panel (NAS/NRC (National Academy of Sciences/Nuclear Regulatory Commission) 1956) developed a DD compromise consensus of 40 R that was strongly influenced by emerging data from mouse radiation geneticist Panel member, William Russell (1951). The Panel's decision was derived from comparisons of radiation-induced mutation rates at seven gene loci in the mouse that were compared with relatively uncertain/crude estimates of spontaneous mutation rates in people. The Panel became intrigued with the mouse data since it suggested that the mouse was about 15 times more sensitive than the fruit fly to the induction of gene mutations by radiation, with concerns that humans may be even more sensitive (Crow 1995).[4]

The 10% value of Muller (1955) (as derived from his 8–16% estimate) for the proportion of human genetic damage/mutation from the cumulative impact of background radiation became widely adopted by leaders in the field. For example, Nobel laureate geneticist Joshua Lederberg emphasized this figure in multiple papers and testimonies, enhancing its acceptance, especially due to his scientific profile. Further, John Gofman and Arthur Tamplin (1970, 1971), leaders in radiation risk assessment at the Lawrence Livermore Laboratory of the US Atomic Energy Commission (AEC), also employed the 10% value in numerous articles, books, and Congressional Hearings in 1969 and the early 1970s (Calabrese 2023). However, Gofman and Tamplin not only applied the 10% figure to the issue of hereditary risk but also to estimate the occurrence of leukemia and other cancer risks. They made risk projections based on these mutational estimates of background radiation adjusted for human longevity applying it directly to human cancer risk assessment from radiation. This methodology also provided a tentative estimate of cancer risks related to nuclear power plant emission standards in the US by the AEC. Gofman and Tamplin estimated that cumulative background radiation had the potential to be responsible for one-tenth (i.e., 32,000 cases) of the 320,000 new cases of leukemia and cancers per year in the US (circa 1970). Nuclear power plant emissions (0.17 rem/year/person) were said to have the potential to double the background radiation mutation number over 30 years. The testimonies, related publications, and other actions of Gofman and Tamplin created major public and scientific debates on the topic (Calabrese 2023). Their actions stimulated the U.S. Congress and the Secretary of Health Education and

Welfare to ensure that the U.S. NAS created the Biological Effects of Ionizing Radiation (BEIR I) Committee in 1970 to assess the claims of Gofman and Tamplin (1970), Gofman and Tamplin (1971). In their report 2 years later, the BEIR I Committee (NAS/NRC (National Academy of Sciences/Nuclear Regulatory Commission) 1972) adopted key underlying assumptions of Gofman and Tamplin about the effects of background radiation and linearity at low doses for mutation and cancer, recommending the adoption of the LNT model for cancer risk assessment. Underlying the actions of Gofman and Tamplin (1970), Gofman and Tamplin (1971) and the BEIR I Committee was the high-profile and authoritative report of the US NAS Genetics Panel (NAS/NRC (National Academy of Sciences/Nuclear Regulatory Commission) 1956) that used the 10% mutation estimate for background radiation as their starting point in developing a DD concept to estimate hereditary risks of radiation exposure. The estimate of the BEAR I Genetics Panel (NAS/NRC (National Academy of Sciences/Nuclear Regulatory Commission) 1956) was largely adopted from the earlier paper of Muller (1955) who was not only highly prominent but also a member of that BEAR I Genetics Panel.

Perspective: More significant limitations of LNT

It is now 70 years since the spate of 1950s estimates concerning the impact of background radiation on hereditary and cancer risks. What has been learned?

The original Muller mistake that led to the creation of the LNT model

The most significant development since the original proposal of Muller for the LNT dose-response model is the understanding that the genome is not stable but is under constant chemical attack, with vast numbers of genetic alterations constantly occurring every second in most cells (Setlow 1988; Lindahl 1996; Lindahl and Barnes 2000). However, Muller came to the erroneous conclusion that the genome was very stable because he was unable to detect the damage since it was repaired so quickly. Thus, the two major mistakes of Muller in developing the LNT concept were: (1) his stable genome hypothesis; and (2) that he failed to propose a range of competing hypotheses that could test the observations. He limited his choices to a single option, and the scientific community followed his lead. That is, the apparently very stable genome could have resulted from very few mutations being induced and not being repaired or from many mutations being induced that were rapidly and efficiently repaired. These two mistakes of Muller were profound and dominated the field for nearly a half-century, and they provided the foundation for the LNT single-hit model that assumed no repair. This was the perspective that guided the discussions and recommendations of the BEAR I Genetics Panel (NAS/NRC (National Academy of Sciences/Nuclear Regulatory Commission) 1956), its LNT endorsement, and the basis of the Environmental Protection Agency (EPA) LNT policy starting in 1975 (Albert 1994).

It has also been learned that the most likely cause of background mutation in humans is endogenous metabolism which produces vast numbers of oxygen radicals. So vast is the generation of these ROS that it is now believed that the DNA repair processes evolved to repair damage from endogenous metabolism (Pollycove and Feinendegen 2003), instead of to repair damage from background radiation, which seems likely given radiation's rather trivial relative contribution. These processes are also framed within the context of biological allometry such that metabolic rate and free radical generation are inversely related to body size and lifespan in mammals. Thus, the durational assumptions of Glass, Muller, Huxley, and others of the 1950s have been trivialized.

It seems strange, and is of particular relevance to the scientific debates in this area of research, that as the vast evidence emerged on the effects of endogenous metabolism on the generation of oxy-radicals and their impact on mutation rates, aging, and cancer, such evidence was essentially ignored by members of the radiation genetics research community, including those at the center of the background radiation mutation debate, such as Muller, Huxley, Glass and the membership of the BEAR I Genetics Panel, Sternglass (1963, 1969) and Gofman and Tamplin. In fact, by 1962 Harman had reported the enormous discrepancy between the levels of oxy-radicals produced by endogenous metabolism and ionizing radiation during the time that this Panel was actively meeting and offering their advisory recommendations.

Other important research developments emerged that also came to challenge the perspective that background radiation had a significant impact on human spontaneous mutation rates and genetic damage-related diseases. The following subsections clarify how contemporary research findings illustrate the multiple evolutionary-based adaptive strategies to preserve

genome integrity, which were not known during the Muller era when the LNT concept and model were developed and background radiation risks were first conceived. Contemporary experimental research has affected experimental understandings of background radiation-induced mutation, and while experimental science is normally "self-correcting", this has not been the case with "regulatory science" as applied to cancer risk assessment.

However, important problems with "regulatory science" have been shown in the LNT-supportive 1977 NAS report of the Safe Drinking Water Committee (SDWC 1977). Essentially, all of the SDWC's underlying LNT assumptions have been shown to be incorrect (see Calabrese 2009, p. 217, Table 4), with regulatory agencies such as EPA simply failing to address these striking developments. Yet, EPA's continued failure to address such important scientific developments ensures that LNT model policy use is unlikely to be legitimately evaluated to reflect current understandings of the science.

Background mutation rates

The per-generation base-substitution mutation rate for humans is about twice the average rate for *Drosophila melanogaster* as well as for *C. elegans* and *Arabidopsis thaliana*. According to Lynch (2010a, 2010b), this pattern of genetic damage indicates that the capacity of natural selection to minimize the mutation rate is compromised since random genetic drift increases in response to reductions in effective population sizes. This occurs in the evolutionary transition from unicellular to multicellular organisms (Lynch 2007, 2008). Furthermore, while humans display a relatively higher per-generational mutation rate/cell division, the human spontaneous germline mutation rate is lower than that reported in any other organisms that have been adequately evaluated. More specifically, based on an assumption of 216 germline cell divisions per generation (with many more in males than in females) in humans, the rate of base substitutional mutation is 0.06 x 10^9 per site/germline cell division, which is about 20% of that in unicellular organisms. Furthermore, in the case of *Drosophila*, in which there are 36 germline cell divisions per generation the per-cell mutation rate in the germline is about 0.13 x 10^9 per site, or double that seen with humans.

The soma disposal hypothesis

In 1977, Kirkwood proposed the soma disposal hypothesis in which he claimed that evolution should select organisms that direct more energy to protect germ cells over somatic cells. In general, this hypothesis has been supported with spermatogonia and oocytes showing about 10- to 100-fold fewer mutations than somatic cells (Lynch 2010a, 2010b). Muller and his colleagues failed to anticipate this possibility as well.

Sperm selection

The process of sperm selection has been intensively studied. Multiple damage screening detection processes operate and ultimately select the few hundred sperm that have realistic chances of fertilization out of approximately two billion per human ejaculation. Thus, such complex screenings detect numerous biological irregularities and target damaged/irregular sperm for apoptosis and elimination (Fitzpatrick and Lupol 2014).

DNA repair processes

Numerous complementary repair processes within oocytes compensate for repair deficiencies in the maturing spermatozoa that are acquired in the process of sperm becoming far more hydrodynamically capable (Fitzpatrick and Lupold 2014). Likewise, there are further increases in repair and selection at the zygote stage (Lynch 2010a, 2010b; Garcia-Rodriguez et al. 2018).

There are also differences among mammalian species in their DNA repair capacity that are a function of species longevity. Thus, longer-lived species tend to have more efficient DNA repair. Whether this applies in a general sense to spermatogonia and oocytes is a research question, but it does apply to somatic cells such as fibroblasts and other cell types (Hart and Setlow 1974).

Gene mutation versus gene deletion: the Key Muller studies

The radiation-induced gene mutation data in fruit flies that served as the basis of the Muller calculation were not gene mutations but phenotypic changes caused by modest to massive gene deletions due to the excessively high doses of X-rays (Calabrese 2017c). These exposures would have exceeded the capacity of repair processes in spermatogonia, oocytes, and zygotes and the very limited repair processes that operate within maturing spermatozoa. Consequently,

the Muller research to evaluate the impact of background radiation on fruit flies and extrapolate these estimates to humans was not appropriate.

The doubling dose concept and its refinement

The gene mutation concept and how it relates to the issue of DD was not established in 1955 when Muller made his genetic damage interspecies extrapolation proposal. However, a year later the BEAR I Genetics Panel (NAS/NRC (National Academy of Sciences/Nuclear Regulatory Commission) 1956) created the DD concept based on spontaneous mutation rates, radiation-induced mutation rates, and their ideas about natural selection. The panel concluded that it would take many generations of continual exposure to a DD of radiation to double the load of genetic mutations in the genome, that is before a new equilibrium would be reached between mutation and natural selection, such that the frequency of mutations/genome in the human population would be twice that found before the first exposure. Gofman and Tamplin (1970) grossly misunderstood and misapplied the concept of DD to their cancer risk estimates by assuming that the doubling would occur following just one generation period of exposed individuals, thereby greatly inflating cancer risks (Calabrese 2023).

Integrating the above information shows clearly that the proposal of Muller that 10% of human gene mutations result from background radiation was not credible, the most important reason being that spontaneous mutations are mostly due to endogenous metabolism and that, despite vast initial damage, the genome remains quite stable over time. Efficiencies in the repair of SSBs and DSBs from radiation and metabolism have been addressed and quantified and also remain stable over time. There has likely been a strong selection for enhanced repair within species that live longer, further diminishing that quantitative excess estimated by Muller (Lynch 2010a, 2010b).

The question of whether there is a threshold dose rate

The major discovery by William Russell et al. (1958) that there is a dose rate effect in mouse stem-cell spermatogonia provided a potentially major reason for questioning the wisdom of adopting the LNT model, especially because of his hypothesis that it might result from the repair of mutational damage[5]. Indeed, he later discovered that repair of mutational damage was much more efficient in mouse oocytes than in stem-cell spermatogonia, which led him (Russell 1967) to write: "Thus, the answer to the question of whether or not there is a threshold dose-rate for mutation induction may turn out to be "no", for mouse spermatogonia, and "yes, for all practical purposes" in mouse oocytes. He further commented that, "when [he and colleagues] started [their] program twenty years ago, it was generally believed that point mutation rate is linearly related to radiation dose, that it is independent of dose rate and dose fractionation, and that there is no repair of radiation-induced mutational damage and no threshold dose or dose rate." He also stated, "Since there appears to be no threshold dose rate for mutation induction in spermatogonia, any radiation exposure involves some genetic risk." After completing the final experiments at ORNL on the dose rate effect in stem-cell spermatogonia at the lowest dose rate ever tested of 0.0007 R/min (i.e., 2000-3000-fold greater than background), Russell and Kelly (1982) provided the last of several statistical analyses that described the magnitude of the dose-rate effect in males. They concluded that within the dose-rate range of 0.8 R/min to 0.0007 R/min, "the mutational response appears to be linearly related to dose ...." and from this analysis concluded that, "the doubling dose based on the low-dose-rate data compiled here is 110 R." At about this same time (Russell 1981) stated that, "in short, it would seem valid, and not an overestimation of genetic risk from irradiation of the male, to assume that there is no threshold dose rate, and that the response is linear with dose at all dose rates below the low ones for which we already have experimental data." Similar statements were not uncommon in later papers. However, even with Russell's "assumption" that there is no threshold dose rate in stem-cell spermatogonia, his estimated doubling dose of 110 R is so high as to suggest that the capacity to detect a significant cancer risk in the low dose zone would be beyond the capacity of epidemiological evaluations. However, as noted earlier in Note c, because of the error of 120%[6] that the Russells admitted to having made in their estimate of the spontaneous mutation rate per generation, a threshold model likely applies in the male (Calabrese 2017a, 2017b) as Russell had concluded earlier it did for females. A related paper (Selby and Calabrese 2023) explains the authors' current view of this matter and why it is now apparent that there is a threshold dose rate in male mice (in stem-cell spermatogonia) and why background radiation is of no practical importance to the background mutation rate in mice.

Negative epidemiology for background radiation

In general, epidemiologic studies have yet to be able to detect effects below approximately 100 millisieverts,

which is far above the background (Ricci and Calabrese 2022). Nonetheless, the relative impact of background radiation and other metabolic causes of mutation remains relatively constant and still reveals that a possible contribution from background radiation, regardless of the species and even over time, is below detection. These findings are consistent with the conclusion of the BEIR III Committee (NAS/NRC (National Academy of Sciences/Nuclear Regulatory Commission) 1980, p. 3) concerning background radiation, which stated, "The Committee does not know whether dose rates of gamma or X-rays of about 100 mrad/yr are detrimental to man … It is unlikely that carcinogenic and teratogenic effects of doses of low-LET radiation administered at this dose rate will be demonstrable … "

Contemporary issues: regulatory bias and inertia

The use of LNT in cancer risk assessment has been highly controversial and extensively debated since its conceptual recommendations by various NAS Committees, starting in 1956 with the NAS BEAR I Genetics Panel and continuing to the present time. A recent Freedom of Information Act-based article in the Junk Science (2023) website provided important information concerning the philosophies and attitudes of leaders in EPA radiation programs and other colleagues concerning scientific challenges to the validity of the LNT model. The article was striking in that it showed the great reluctance of regulatory leaders to consider scientific challenges to current LNT policies, which were considered "set in stone". The Junk Science article raised important questions concerning the capacity of the EPA to fairly and properly address scientific challenges to its LNT-based policy for cancer risk assessment.

Conclusion

Cancer and hereditary risk estimates due to background radiation became a central feature in the development and application of radiation risk assessment that affected the public perception and policy developments within the US and other countries (Sankaranarayanan and Wassom 2008). A spectrum of converging lines of evidence (i.e., endogenous metabolism dominating background radiation in terms of free radical production, efficient DNA repair, germ cell mutation rates) contradict the estimates of Muller, his contemporary experts, the BEAR I Genetics Panel, Gofman and Tamplin, and others. Epidemiological studies overwhelmingly confirm the negligible impact of background radiation. This analysis indicates that the bases for these predicted background responses were fundamentally incorrect. Yet, these assumptions became dominant due to the fear-generating influence of Muller, the BEAR I Genetics Panel, the publicity of the Sternglass (1963, 1969) and Gofman and Tamplin (1970), Gofman and Tamplin (1971) and later, the NAS BEIR Committees, and these assumptions have profoundly impacted EPA carcinogen regulatory policy to the present time, with other countries following their lead (Blackburn 2021). The question remains as to how regulatory science-based decision-making can be self-corrected as new findings emerge. To date, regulatory agency "science" is a striking anomaly as far as traditional science is concerned. That is, it shows a limited capacity for self-correction even when confronted with convincing contrary data when governed by a preset political or ideological narrative. Recent striking discoveries of high-level EPA regulatory official emails have confirmed this agency-based ideological, rather than scientific, "leadership" (Junk Science 2023). See Jonathan Edwards, 5 August 2015 email—Edwards is the Director of EPA's Office of Indoor Air and Radiation. The article reports that "Edwards states his office would never subscribe to opening up the LNT policy for review and that it is "set in stone" EPA Policy" (Junk Science 2023). This perspective clearly illustrates why "regulatory science" is often not capable of self-correction. Yet, EPA administrators often publicly emphasize that their policies are science-based. When a policy is "set in stone" it will never have the chance to be "self-correcting", which is a fundamental characteristic of real science.

Notes

1. Based on numerical linear extrapolation, Muller (1955) asserted there was background mutation incidence due to radiation in his fruit fly model. Yet, other researchers, such as Stadler (1930), had provided plant dose-response data using nine doses with the lower three having no treatment effect, leading to his suggestion of a threshold. Likewise, Giles (1940) administered radiation some 1,000-fold greater than the background without detecting any genetic damage increase above the background in *Tradescantia*. He also showed that this same high dose had no impact on plants with very low or very high background mutation rates. Giles (1940) concluded that "natural radiation is very rarely involved in the production of spontaneous chromosome aberrations". Several groups of researchers supported the findings of Giles (1940) using the fruit fly model of Muller. In these studies, Warren P. Spencer (1935), who later was a key collaborator with

Muller and Curt Stern on the Manhattan Project radiation genetics mutation research, reported that the feeding of fruit flies with a diet of very high levels of carnotite, a radioactive ore, failed to induce mutation in extensive studies. Also, in other experiments, fruit flies were transported from 70,000-100,000 feet above the earth to enhance the exposure to cosmic rays for 6-16 hours, increasing the exposure rates by about five-fold. These exposures failed to increase the frequency of either recessive lethals or translocations, and they found no breaks in the X-chromosome (Pipkin and Sullivan 1959; Reddi and Rao 1964), thereby not supporting the background radiation assumption of Muller (1955).

2. Readers interested in assessing comprehensively the historical foundations for why the LNT model was adopted should see Calabrese (2019).

3. Muller was one of nine radiation geneticists who provided estimates of radiation-induced mutations from 10 R to the BEAR I Genetics Panel in February 1956. A copy of Muller's (1956a) analysis dated 25 February 1956 provides a detailed estimate of the number of mutations per 160,000,000 people, the approximate US population at that time. The report of Muller to the BEAR Panel was a seven-page, single-spaced detailed assessment of this issue, providing far greater detail than the Muller (1955) paper. Based on the Muller (1955) paper and his letter to the BEAR I Genetics Panel (Muller 1956a), both of which strongly promoted the doubling dose (DD) concept, there is the unavoidable, yet tentative, conclusion that Muller's views strongly influenced the BEAR I Genetics Panel DD concept, even though the Panel report (NAS/NRC, 1956) did not cite Muller's article/letter or other possible sources of influence. At the core of the DD concept was the long-standing belief in the radiation geneticist community that induced mutations by radiation and other causes were not repairable (Muller 1929). In fact, the LNT single-hit model of Timofeeff-Ressovsky et al. (1935) failed to include a repair component. The belief in a lack of genetic damage repair was first challenged by Russell et al. (1958) in their groundbreaking paper on mouse spermatogonia and oocytes.

4. Note that the BEAR I Genetics Panel refused to evaluate the major study of genetic mutation in the offspring of survivors of the atomic bomb explosions in Japan that was offered to the Panel by Panelist James V. Neel. See Calabrese (2020) for a detailed assessment of this matter. Furthermore, the 15-fold greater sensitivity of the male mouse was later shown to be based on a control group error of 120% (Calabrese 2020b). Correction for this error at that time would likely have had a major impact on Panel estimates, leading to a threshold model. The reader is directed to a recently published paper on the Russell mouse mutational historical foundations, errors, and their risk assessment implications (Selby and Calabrese 2023).

5. The dose-rate discovery was considered a major development since before that paper, it was long believed that all radiation-induced damage was cumulative, irreversible, and unrepairable (Calabrese 2019). So significant were these findings perceived that they prompted Hermann Muller to change his laboratory research direction to assess this dose-response phenomenon in fruit flies. In 1972, the NAS BEIR I Genetics Committee (1972) acknowledged the need to incorporate the dose rate concept into risk assessment based on Russell et al. (1958) and subsequent findings.

6. In a 1997 follow-up paper (Russell and Russell 1997), Russell and Russell acknowledged an error in their 1996 PNAS paper (Russell and Russell 1996) by publishing a correction factor to account for their earlier failure to report and deal with large clusters of mutations. As explained in a recently published paper (Selby and Calabrese 2023), the required correction factor is likely to be at least 160% instead of the 120% proposed by Russell and Russell.

Disclosure statement

The authors report there are no competing interests to declare. The U.S. Government is authorized to reproduce and distribute for governmental purposes notwithstanding any copyright notation thereon.

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