Arch Toxicol (2013) 87:1621–1633
DOI 10.1007/s00204-013-1104-7

REVIEW ARTICLE

Origin of the linearity no threshold (LNT) dose–response concept

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Received: 15 March 2013 / Accepted: 11 July 2013 / Published online: 26 July 2013

Abstract This paper identifies the origin of the linearity at low-dose concept [i.e., linear no threshold (LNT)] for ionizing radiation-induced mutation. After the discovery of X-ray-induced mutations, Olson and Lewis (Nature 121(3052):673–674, 1928) proposed that cosmic/terrestrial radiation-induced mutations provide the principal mechanism for the induction of heritable traits, providing the driving force for evolution. For this concept to be general, a LNT dose relationship was assumed, with genetic damage proportional to the energy absorbed. Subsequent studies suggested a linear dose response for ionizing radiation-induced mutations (Hanson and Heys in Am Nat 63(686):201–213, 1929; Oliver in Science 71:44–46, 1930), supporting the evolutionary hypothesis. Based on an evaluation of spontaneous and ionizing radiation-induced mutation with *Drosophila*, Muller argued that background radiation had a negligible impact on spontaneous mutation, discrediting the ionizing radiation-based evolutionary hypothesis. Nonetheless, an expanded set of mutation dose–response observations provided a basis for collaboration between theoretical physicists (Max Delbruck and Gunter Zimmer) and the radiation geneticist Nicolai Timoféeff-Ressovsky. They developed interrelated physical science-based genetics perspectives including a biophysical model of the gene, a radiation-induced gene mutation target theory and the single-hit hypothesis of radiation-induced mutation, which, when integrated, provided the theoretical mechanism and mathematical basis for the LNT model. The LNT concept became accepted by radiation geneticists and recommended by national/international advisory committees for risk assessment of ionizing radiation-induced mutational damage/cancer from the mid-1950s to the present. The LNT concept was later generalized to chemical carcinogen risk assessment and used by public health and regulatory agencies worldwide.

Keywords Ionizing radiation · Linearity · Dose response · Risk assessment · Threshold dose response · Target theory · Eugenics · LNT

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Introduction

In 1956, the US National Academy of Sciences (NAS) Committee on Biological Effects of Atomic Radiation (BEAR I)/Genetics Panel issued the most far reaching recommendation in the history of risk assessment that genomic risks associated with exposure to ionizing radiation should be evaluated with a linear dose–response model, no longer via the threshold dose–response model that had long been the "gold" standard for medicine and physiology (Calabrese 2005, 2009a, 2011). The Genetics Panel members believed that there was no safe exposure to ionizing radiation for reproductive cells with the mutation risk being increased even with a single ionization (Hamblin 2007). The LNT concept was generalized in 1958 to somatic cells and cancer risk assessment by the National Committee for Radiation Protection and Measurement (NCRPM) (Whittemore 1986). Quickly thereafter, other national and international advisory committees and organizations adopted such judgments for ionizing radiation (Calabrese 2009b). In 1977, the Safe Drinking Water Committee (SDWC) of the US NAS extended the linear dose–response risk assessment model of the BEAR/

Biological Effects of Ionizing Radiation (BEIR) committees to chemical carcinogens, a recommendation that was soon adopted and implemented by the Environmental Protection Agency (EPA). On a parallel track, similar LNT risk assessment procedures were adopted by the Food and Drug Administration (FDA) in 1977 concerning animal carcinogen drug residues.

Despite the fact that the LNT model has been of central importance in chemical and ionizing radiation regulatory risk assessment, its origin is not within the environmental/occupational risk assessment domain. The current paper provides a novel historical assessment of the scientific origin of the LNT. It will show that the LNT was first applied to the field of biology in 1928 to explain the occurrence of genetic variation that would serve as the "biological engine" for evolution. The paper will also demonstrate how the linear dose–response model as proposed by Olson and Lewis (1928), which soon afterward became transformed into a "Proportionality Rule" by Muller (1930), became mechanistically framed within the context of a single-"hit" hypothesis based on the target theory by Timoféeff-Ressovsky et al. (1935) in a unique collaborative effort between leading theoretical physicists and radiation genetics. This paper extends two earlier publications within Archives of Toxicology concerning historical foundations of the LNT concept (Calabrese, 2009b) and threshold/hormetic (Calabrese 2009a) models.

Evolution and LNT

Since the publication of the Origin of Species in 1859 by Darwin and the rediscovery of the works of Mendel on gene inheritance, there was intense interest in the biological community to determine the cause of genetic change or novelty that would be subject to natural selection, thereby providing an important mechanism of evolution. As noted by Patterson (1933), a well-known colleague of Hermann J. Muller at the University of Texas/Austin, "the important question in biology is the problem of evolution" referring to the need to understand the mechanism of evolution at the gene level. Despite the fact that the gene was more of a concept than a physical entity during the early decades of the twentieth century, it was widely believed that the gene was the basic unit of heredity and that the driving force for evolutionary change must be via the induction of heritable genetic changes or mutations at the gene level (Muller 1922). This perspective provided the basis for intense interest by numerous genetics researchers in the second and third decades of the twentieth century to induce alterations in heritable traits by environmental (e.g., temperature) alterations, physiological stressors (e.g., starvation), as well as toxic chemicals and ionizing and non-ionizing radiation.

Given the central importance of evolution in biology and underscoring the intensity of the competition to be the first to demonstrate inducible heritable changes, Muller (1927) provided only an initial "discussion" of his mutagenicity findings with no data in his now famous *Science* paper that led to his Nobel Prize in 1946. This was done in order to secure recognition of being the first to report induction of heritable mutations by an environmental agent (i.e., X-rays). The supporting data were published the next year in a conference proceeding of very limited distribution based on the World Cat database (Muller 1928a) and also within the *Proceedings of the National Academy of Sciences* (PNAS) (Muller 1928b). Not only were the findings of mutation significant so too was the fact that the mutation rate was increased by about 150-fold at the highest dose tested.

Muller speculated that naturally occurring ionizing radiation might be a significant explanatory factor for genetic variation and may drive the evolution process. However, Muller was cautious in making the mutation–evolution link as the doses he had used to induce mutation were extremely high, exceeding background by about 200,000-fold, causing sterility or mortality in a substantial proportion of the fruit flies tested. In addition, the dose response was not linear but closer to a square root function due to a modest decline from linearity at the highest dose (Muller 1927, 1928a). If the true dose response for ionizing radiation-induced gene mutation was linear at low dose, as a general condition, then it may have explanatory implications for an evolution mechanism. Consequently, he soon directed several members in his laboratory to assess the topic of dose response more fully than he did in his groundbreaking mutation discovery. While the follow-up research by Muller's group was being undertaken, Axel R. Olson and the prestigious physical chemist Gilbert N. Lewis (1928) of the University of California/Berkeley published a proposal on April 28, 1928, in *Nature* that natural radioactivity was likely a significant cause of mutation that could generate variability from the parent generation and affect the process of evolution. These authors based this supposition on a report of January 1, 1928, in *PNAS* by Goodspeed and Olson on X-ray-induced heritable changes in tobacco. These authors claimed that the tobacco plant studies were specially planned to facilitate a direct comparison of mutation rates between the artificial X-rays and "naturally occurring radiations." Olson and Lewis (1928) also stated that "since the rays can only be effective when they are absorbed, and this produces ionizations, it seems safe to assume that the various rays will produce biological effects *in proportion to the ionization which they cause*" (emphasis added), a perspective based on the emerging target theory for radiation-induced biological effects proposed by leaders in the physics community (Glocker 1927; Crowther 1924).

Olson and Lewis (1928) then utilized a simple linear mathematical model to derive a mutation estimate at a selected natural background radiation dose. With this method, they estimated the number of variants (mutants) induced per year by natural radiation. These authors concluded that "it seems, therefore not altogether extravagant to assume that such variations as actually occur in nature are due largely to the radioactivity of the environment." The involvement of Gilbert Lewis in this activity, while unexpected, was derived from his research in the 1920s in the area of radiation physics (Coffey 2008). Furthermore, his eclectic research activities had also drawn him toward evolutionary theory, the subject of his major presentation (i.e., Silliman Lecture) at Yale, just preceding the development of the LNT paper in *Nature* (Lewis 1926). This lecture followed that of Thomas Hunt Morgan of Columbia University in 1925, Muller's Ph. D. advisor and 1936 Nobel Prize recipient. The perspective of Olson and Lewis (1928) was also independently advanced by Muller in a paper read before the National Academy of Sciences on April 24, 1928, and published on September 14, 1928. The statement of Muller (1928b) was principally conceptual, lacking the detailed formulation of Olson and Lewis (1928).

The following year, Babcock and Collins (1929a, b) tested the hypothesis of Olson and Lewis (1928). They found a location in which the natural radiation was twice that found in their University of California/Berkeley laboratory. Using the ClB strain sex-linked recessive *Drosophila* assay, they reported an increase in mutation that corresponded in the same proportion as the difference in background radiation, supporting the proportionality hypothesis. Detailed experimental methods including the actual radioactivity levels were never published, although such data were promised to be provided in a subsequent paper. In 1930, Hanson and Heys provided further support for the hypothesis that "natural radiation may be responsible for the mutations that are the grist of the natural selection mill with the resulting evolution of new forms." Their findings were based on a study of fruit fly mutations in an abandoned carnotite (i.e., uranium) mine. Such interpretations were initially supported by commentaries by various authors (Lind 1929; Dixon 1929, 1930).

In 1930 Muller and Rice University physicist, Mott-Smith, challenged this LNT evolution perspective by reporting that natural radiation, which was of such a low-dose rate, could only account for about 1/1,300 of the gene mutations that occurred spontaneously in *Drosophila melanogaster*, assuming a linear dose response. The authors concluded that other causes must explain the origin of most mutations that spontaneously occur. Nonetheless, in his dissertation, under the direction of Muller, Oliver (1931) stated that cosmic and terrestrial radiations must account for some proportion of the spontaneous mutations (see Muller 1930). This conclusion was justified on the belief that the response is linear at low dose, with there being no threshold for a mutation response. This relationship was stated as holding true for all types of high-energy radiation (e.g., gamma, beta, X-rays and probably ultra-violet rays). Thus, Oliver (1931) concluded that "by inference it can be added that the cosmic and the terrestrial radiations also are capable of producing mutations in proportion to their power of ionization." Oliver (1931) also extended the concept of proportionality to chromosomal inversions and translocations further arguing for the support of a background radiation influence. For example, Muller and Altenburg (1930) noted that translocations are induced at a similar frequency as gene mutations. Given these circumstances, Oliver (1931) noted that "one would expect each of the classes of changes considered to occur with the same frequency when the individuals are subjected only to the natural conditions, if natural radiation can account for all mutations…" Despite this interpretation of environmental radiation-induced genetic changes, Oliver (1931) concluded that "some other condition must, therefore, enter in order to explain the difference in non-radiated material, between the frequency of gene mutation and that of the other type of genetic changes." (p. 34)

Even though Muller dismissed natural radiation as providing a quantifiably significant mutational influence to derive genetic novelty for evolutionary change, he still retained his belief in the linear dose–response relationship (p. 238) (Muller 1930) based on the findings of Hanson and Heys (1929, 1930) and Oliver (1930). Even though the hypothesis of Olson and Lewis (1928) did not maintain significant support for long within the scientific community, Muller and other leaders of the radiation genetics community became strong advocates of the LNT model to account for genomic mutations and the occurrence of cancer.

It may seem difficult to understand in retrospect why prominent scientific leaders such as Gilbert N. Lewis, Hermann J. Muller and others so quickly adopted a belief in linearity at low dose. In the case of Muller, he was fully committed to this view after the publication of only three studies (Hanson and Heys 1929, 1930; Oliver 1930) in which the lowest cumulative dose was roughly 285 r, administered in an acute manner, the rough approximation of 1,000 modern chest X-rays in 3.5 min or 5 chest X-rays/s.

In his rather copious publications during this period of "belief"/concept formulation, Muller never addressed contemporary publications that did not support a linear interpretation (Patterson 1928; Weinstein 1928; Stadler 1930, 1931). Yet, he was well aware that the lowest doses in the Hanson and Heys (1929, 1930) and Oliver (1930) papers were acute studies that grossly exceeded background radiation exposure. To think within a linear dose–response term

framework ran counter to pharmacological and chemical toxicological experience at that time. As Zimmer (1966) reflectively wrote, toxic chemicals in the early decades of the twentieth century demonstrated "no effect up to a threshold dose and then climbed steeply up to 100 %." Muller and others argued that the genetic response to ionizing radiation demanded a different evaluative framework.

Target theory and LNT

A likely explanation for Muller's (and possibly Gilbert N. Lewis's) acceptance of the LNT in the absence of convincing dose–response data may be found within the scientific culture at the time. X-ray-induced mutational effects were placed within the context of what was called the radiation target theory. This theory was quantitative and dosimetric, with mathematical calculations related to quantum mechanics, reflecting the leadership of prestigious theoretical physicists (von Schwerin 2010). The formation of a physics-based target theory was established prior to the discovery of inducible mutations by Muller (1927) by medical physicists such as Dessauer (1922), Glocker (1927) and Crowther (1924, 1926, 1927), setting the stage for a novel scientific framing of the mutational data in the 1930s. The mutation findings of Muller (1927) were a major scientific advance that easily fit into the target theory concept while also markedly advancing the scientific standing of target theory itself.

The radiation target theory as applied to mutations was formulated by the detailed interactions and collaborations of leading radiation geneticists and theoretical physicists during the mid-1930s. During this time, radiation geneticists, lead by Nicolai Timoféeff-Ressovsky, and physicists, including Niels Bohr, with a profound interest in the interface of physics and biology, would meet each year, typically in Copenhagen and Belgium for extensive discussions. From these exchanges developed the seminal conceptual paper by Timoféeff-Ressovsky and the physicists Max Delbruck and Kevin Gunter Zimmer (Timoféeff-Ressovsky et al. 1935) that would establish a conceptual framework for gene structure, target theory for the induction of mutations via ionizing radiation, the single-hit mechanism hypothesis to account for the shape of the LNT dose response and the application of this dose–response model for what was to become modern cancer risk assessment. The genetic target theory saw mutation as a purely physical action following an all or none law in which a single ionization or energy absorption produces the mutational effect independent of all other ionizations and energy absorptions.

This linearity feature stands in contrast to normal physiology that invariably deals with large numbers of molecules of each kind, and where the elimination of a single molecule would not result in observable effects (Delbruck 1940). The energy of ionizing radiation was assumed to be essentially transformed into a genetic effect. According to the physicist turned biologist Max Delbruck (1969 Nobel Prize recipient in Biology and Medicine), the proportionality rule that was proposed earlier by Muller, based on the research of Hansen and Heys (1929) and Oliver (1930, 1931) and supported in experimental research by Timoféeff-Ressovsky et al. (1935), provided the basis of the single-hit mechanism interpretation and the calculation of the size of the gene (Delbruck 1940). Table 1 provides a listing of quotes in which the early conceptual framing of the dose–response proportionality concept occurred. The transforming of a dose–response hypothesis based on a very limited amount of data into a biological "Rule" by Muller was done without significant discussion of the concept, its possible mechanisms as well as the recognition of data that may contradict this "Rule."

Although Muller was a geneticist, he was drawn quickly toward the physics-mutation interface, accepting significant elements of target theory for radiation-induced mutational effects, including the important assumptions that damage was proportional to the energy absorbed, linear dose–response modeling and that effects were cumulative and deleterious (Muller et al. 1936). Muller knew Timoféeff-Ressovsky, having met him in the Soviet Union in 1922, encouraging him and his colleagues to transform his laboratory to one of the *Drosophila* genetics. Muller renewed contact with Timoféeff-Ressovsky during the 5th International Congress on Genetics in 1927. From November 1932 to September 1933, Muller researched in Berlin with Timoféeff-Ressovsky. He also participated in the physics-biology/mutation discussions in Copenhagen in 1936, engaging Niels Bohr and other leading physicists. Experiments of radiation geneticists during this period were often designed within the context of this target theory framework. This was also the case for critical studies performed a decade later under the aegis of the Manhattan Project at the University of Rochester under the direction of Curt Stern (with Muller serving as a consultant) (Spencer and Stern 1948; Caspari and Stern 1948).

The hit hypothesis

As noted above, in his Nobel Prize research, Muller reported that the induction of mutations was not directly proportional to the X-ray dose, but rather to the square root of the dose (Muller 1927). Based on discussion with the physicist and future Nobel Prize winner Irving Langmuir (1932 Nobel Prize in Chemistry), Muller (1927) stated that this observation suggested that the induction of mutation was not caused directly by a single quantum of energy.

Table 1 Documentation of the introduction of the proportionality rule concept into the mutation literature, 1929–1960

References	Quote
Hanson and Heys (1929)	"It is only to be expected that the number of mutations be directly *proportional* to the number of rays to which the organisms are exposed." Page 207
Muller (1930)	"Since then Hanson, using radium, and Oliver in our laboratories using X-rays, have both found that the frequency of mutations produced is exactly *proportional* to the energy of the dosage absorbed… There is, then, no trace of a critical or threshold dosage beneath which the treatment is too dilute to work." Page 236
Oliver (1930)	"That is there is a direct *proportionality* between the percent of lethals and the length of time of treatment may be seen more readily by a comparison of the t_1 values calculated from the results for each of the given doses." Page 45
Stadler (1930)	"Mutation frequency increased approximately in direct *proportion* to dosage." Page 13
Hanson et al. (1931)	"Taking the amount of ionization in air as a measure, the mutation rate seems to vary approximately in direct *proportion* to the intensity." Page 142
Oliver (1931)	"By inference it can be added that the cosmic and the terrestrial radiations of higher energy content also are capable of producing mutations in *proportion* to their power of ionization." Page 480
Oliver (1931)	"The relation of *proportionality* to the dosage applies not merely to the lethals in general, but, more specifically, to the lethal gene mutations." Page 485
Oliver (1931)	"…[gene mutations and gene rearrangements] all probably occur in direct *proportion* to the dosage, no matter how small a dose is used." Page 486
Patterson (1931)	"In general their results [i.e., Hanson and Heys 1928 and Oliver 1930] justify the conclusion that the rate is directly *proportional* to the dosage employed." Page 133
Hanson and Heys (1932)	"Further evidence of the *proportionality rule* from a study of the effects of equivalent doses differently applied." Page 335
Hanson and Heys (1932)	"Experiments planned with a view to determining within what limits the *proportionality rule* holds show again a strict correspondence existing between the amount of radium administered and the consequent biological effect, the induced mutation frequency obtained varying directly with the dosage." Page 343
Hanson (1933)	"The rate seems to be directly *proportional* to the dosage. Muller has named this the '*proportionality rule.*' For example, when all other factors are kept constant, doubling the time of exposure also doubles the number of lethal mutations." Page 486
Oliver (1934)	"The frequency of induced mutations is directly *proportional* to the intensity of the treatment." Page 391
Delbruck (1940)	"The *proportionality rule* gave the basis for the single-hit interpretation…" Page 359
Stern (1950)	"The *proportionality rule* has been proven to hold over a wide range. Figure 155 shows that, for Drosophila, the relation is essentially linear over the range from 25 r to several thousand r. It has further been shown that the frequency of induced mutations is independent of the time over which the radiation is applied." Page 433
Stern (1960)	"It has been established for a variety of experimental organisms that the number of mutations induced by radiation is proportional to the dose. This *proportionality* has been proven to hold over a wide range of dosages." Page 491

However, subsequent exposure experiments by Hanson and Heys (1929), Oliver (1930, 1931) and later by Timoféeff-Ressovsky et al. (1935), even though all experiments were at very high dose, supported a proportionality relationship, which was consistent with the "hit" theory of mutation in which the X-ray treatment excites an electron in the target gene. This excitation was proposed to affect a permanent change or mutation to a different molecular structure. Ionizing irradiation was the only effective way to induce mutations; it showed no threshold, suggesting that the absorption of radiation is a quantized and additive process (von Schwerin 2010). A "quantum-jump" was considered to be the physical process caused by a hit on a target, resulting in mutation. Treatment effects induced by a physical agent like ionizing radiation were believed to be caused by one or several discrete biophysical events, that is, hits on a target. Based on hypotheses about what constituted a hit, statistical models were used to construct dose–response relationships. If there was only a single hit on a single target, the dose response was linear. As the number of assumed hits increased, a more threshold like the dose response would appear. In a practical sense, the mathematical model-derived dose response based on an assumed number of hits could be visually matched against the laboratory-obtained dose–response curve. Using this direct and simplified approach, researchers like Muller, Timoféeff-Ressovsky and participating physicists decided the theoretical number of hits. This type of target theory was especially strong in Germany, with support from leaders such as Boris Rajewsky (Director of the KWI for biophysics, 1936), Timoféeff-Ressovsky and others (von Schwerin 2010). This conceptual framework led to the conclusion that mutation was a

single-hit process, proceeding from a single ionization, from a quantum of ionizing radiation in a specific sensitive zone of the gene.

This theoretically based perspective became not only a workable model but a firm belief within the radiation genetics community even though there was no knowledge of the physical nature of the gene. As coauthor of the Timoféeff-Ressovsky et al. (1935) paper, Delbruck subsequently noted in his Nobel Prize lecture that it was thought that genes were very stable and, therefore, showed characteristics of molecules. However, the gene concept at that time was simply that of Mendelian algebraic rates, lacking structural chemistry insight. There was much speculation of gene structure including that of submicroscopic steady-state systems or even an entity not readily analyzable in chemistry as proposed by Bohr (1933).

The paper of Timoféeff-Ressovsky et al. (1935), as noted above, was striking in its collaboration between physics and genetics, its proposed chemical nature of the gene, size of the gene and in the proposal of a "hit" hypothesis as the foundation of the linear dose response for ionizing radiation-induced mutation. While the gene structure and size framework would be bypassed and replaced by the DNA structure of Watson and Crick (1953), the hit theory component of Timoféeff-Ressovsky et al. (1935) was accepted and implemented by the radiation genetics community. The term "hit hypothesis" became commonly used in the lexicon of radiation genetics, including those comprising the BEAR I Committee/Genetics Panel that recommended changing to a linear model from a threshold model for assessing mutation risks from ionizing radiation (Calabrese 2013).

The impact of this 1935 article was facilitated by the actions of Timoféeff-Ressovsky who sent reprints to key researchers. However, the overall immediate impact of the paper was very limited as it was published in an obscure Gottingen journal that was not cited in any leading index with only four issues being printed before ceasing publication. This paper, which provides the origin of the single-hit hypothesis to support a linear dose–response model, was not even cited in the BEAR I report that implemented the concept. Yet, the term "hit" hypothesis and target theory became commonly used, even if credit was not often given to the original paper (Timoféeff-Ressovsky et al. 1935). Nonetheless, this paper did receive a major endorsement in the 1944 book *"What is Life"* by Erwin Schrodinger, a Nobel Prize physicist (1933), raising its visibility in the physics community.

The concept of the gene and its striking stability suggested it must have a unique atomic composition. Delbruck (1970) believed that such stability might be due to each atom of a gene being fixed in its mean position and electron-stable, sunk in an energy well, now seen having stability due to the function of the hydrogen bond. Mutations of such genes could only occur following the absorption of high energies as from ionizing radiation, not from heat under physiological conditions. In fact, a modest increase in vibrational energy was estimated to increase the atomic stability, decreasing mutational risk. Since a transaction in an atom can be affected by a single digit eV and that the initial impact of an X-ray can be several fold greater, it was believed that any gene would be at risk for mutation from radiation. Since the initial energy of impact exceeds a threshold energy of activation, ionizing-radiation should affect not only the induction of a localized mutation but also that of a broad range of gene targets.

The mutation hit theory was challenged by Caspari and Stern (1948) in a chronic, very low-dose rate study, leading to the hypothesis that either a threshold exists or multiple independent primary actions are required for a mutation to occur, or that a recovery or repair effect/process occurred at a very low-dose rate (Howarth et al. 1950; Key 1951). Over the next several decades, the dominance of the physics-based target theory would yield to improved chemical/biological/physiological understandings of the mutation process, including such modified target theory effects of ionizing radiation as DNA repair (in reproductive and somatic cells), adaptive response, the bystander effect as well as the recognition that the biological effects of ionizing radiation are principally due to the generation of hydroxyl radicals/hydrated electrons from cellular water and their migration to cellular targets (Collinson et al. 1962; Czapski and Schwartz 1962; Weiss 1944). In fact, even as the target theory was being applied to mutation by Timoféeff-Ressovsky et al. (1935), the recognition of repair processes, including DNA repair, were emerging (Hanawalt 1994). Such challenges to the hit theory would eventually be brought to the BEAR Committee by Russell (1956, 1963) from Oak Ridge, but only after the BEAR 1 Committee made its linearity recommendation.

Edward Lewis (1957a), another radiation geneticist Nobel Prize (1995) recipient, published a very influential *Science* article in 1957, strongly supporting a linear relationship for cancer, relying on linearity data in the Uphoff and Stern (1949) paper. In subsequent Congressional Testimony, Lewis (1957b) would argue that the dose response was linear, regardless of the mechanism, and should be accepted as such whether or not a mechanism could even be discerned. These comments of Lewis suggested that he recognized the growing mechanistic challenge to the single-hit theory as well as new conceptual problems (e.g., multiple biological processes could yield a linear relationship that did not require a single-hit process) emerging from the physics and genetics communities, including Zimmer (1941), a coauthor of the Timoféeff-Ressovsky et al. (1935) paper and radiation biologists/geneticists (Haas et al. 1950;

Kimball 1952). However, the time period within which Muller's mutation findings were produced was one of the cultural scientific dominance of physics. Association with the leadership of the physics community served to enhance the significance of the mutational findings and its assumed linearity at low dose, as well as providing Muller with an expanded scientific and cultural context that recognized his achievements and enhanced his scientific reputation.

The influence of the hit concept of Timoféeff-Ressovsky et al. (1935) was facilitated via subsequent publications of Lea (1940, 1946), which offered further justification for the target theory-based LNT-single-hit hypothesis for mutation. The publications of Lea were not only authoritative extensions of Timoféeff-Ressovsky et al. (1935) but more readily available than the Timoféef-Ressovsky et al. (1935) paper with its publication in a defunct journal.

Regulatory agency actions

Ionizing radiation

In the radiation risk assessment area, two endpoints were adopted to which linearity was applied: germ cell mutations and cancer. In the case of germ cell mutations, based on several publications in the early 1950s by Muller (1951, 1954), the BEAR I Genetics Panel (1956) proposed to limit exposure to ionizing radiation such that exposure would not exceed doubling of background mutations from conception through the first 30 years of life. The panel assumed that exposure to ionizing radiation could cause mutations to germ cells in a linear manner and had the potential to cause adverse genetic effects in individuals and future generations. The panel derived a risk assessment methodology for application to both first-generation offspring and total genetic risk, including future generations. The panel derived a doubling dose method (i.e., the dose of ionizing radiation, assuming linearity at low dose, that would equal the number of mutations resulting from background exposure), to estimate population-based risks. This doubling dose methodology would predict the number of genetic diseases based on three parameters: the assumed doubling dose, the proposed exposure limit and the background incidence of genetic disease. Based on this risk assessment framework, the panel recommended a "uniform national standard" such that the members of the general population would not receive more than a cumulative dose of 10R from conception through 30 years. This basic method of the BEAR I Committee, using the doubling dose/linear framework, has been refined with recent advances allowing one to integrate between rates of radiation-induced mutation based on mouse studies and the risk of inducible genetic disease in people [Sankaranarayanan and Chakraborty 2000a, b; Sankaranarayanan and Wassom 2008 (see Lyon 2003 for an alternative view)].

In the case of somatic effects, cancer risks were estimated via the use of a linear dose–response model. Assuming linearity to zero, it was estimated that exposure of one rem to one million people each year would cause one to two new cases of leukemia on an annual basis for first decade of life (ICRP 1962; Sowby 1965; UNSCEAR 1962, 1964). As with chemical carcinogenesis risk assessment, therefore, the foundations of the LNT modeling for ionizing radiation-increased cancer risks are directly traced back to Lea, Timoféeff-Ressovsky et al. and ultimately to Muller's proportionality rule.

Chemical carcinogens

Five years after the publication of the BEAR 1 report, Mantel and Bryan (1961) published their influential paper entitled "Safety' Testing of Carcinogenic Agents" based on the probit dose–response model in order to estimate tumor incidence for carcinogens. Biostatistical estimates of cancer risks were first provided by Bryan and Shimkin (1943) when they applied the probit model to estimate the cancer risk of three carcinogenic hydrocarbons (i.e., 20-methylcholanthrene; 1,2,5,6-dibenzanthracene; 3,4-benzpyrene) in strain C_3H male mice.

The motivation for Mantel and Bryan to develop the biostatistical model for predicting carcinogen risk was due to the fact that Mantel, a biostatistician at the US National Cancer Institute (NCI), was asked by the Director of the NCI to develop guidelines for the number of laboratory animals that would be needed to establish the safety of a test agent within the context of a hazard assessment. This response followed a request, after the Thanksgiving cranberry scare of 1959, by the Secretary of the Department of Health, Education and Welfare (HEW) to the NCI. The cranberry scare was a public relations nightmare in which trace residues of a cancer-causing herbicide [i.e., amitrole (3-amino-1,2,4-triazole)] were detected in some sources of cranberries just before the holiday. The secretary of HEW recommended against buying cranberries that year, leading to a consumer panic that threatened the industry. In order to avoid such situations in the future, the secretary of HEW requested the NCI to provide guidance on which cancer-causing substances were "safe" and at what dosage levels.

Mantel and Bryan (1961) noted the generality of their modeling approach and proposed the concept of a virtually safe dose with an estimated risk of 1/100 million. Some 12 years later, the FDA would propose the use of the Mantel-Bryan (1961) model and recommend the 1/100 million safety guide in their July 19, 1973 risk assessment proposal in the Federal Register. When the rule was finalized in

1977, the Mantel-Bryan probit model was retained but with several modifications and with the acceptable (de minimus) risk being reduced to 1/million. This value was considered as the level below which no additional regulatory action would be taken within the context of the safety of animal carcinogen residues. The finalized Mantel-Bryan model of the FDA was the first quantitative risk assessment model approved by a regulatory agency. Two years later, the FDA (1979) significantly revised the cancer risk assessment policy, replacing the modified Mantel-Bryan model with a linear dose–response model based on multiple factors, including its more conservative risk estimation and ease of calculations (Anonymous, 1979). In the low-dose zone, the one-hit model discussed above is closely approximated by a simple linear model.

The US EPA strategy for assessment and regulation of carcinogens displayed a profound evolution during the 1970s. Based on expert testimony during pesticide hearings, EPA attorneys developed a legal brief that embodied "cancer principles" (NAS 1983). These "principles" suggested that carcinogen exposures should be prevented. As the concept of "banning" carcinogenic agents was soon seen as unrealistic, EPA quickly adopted non-regulatory guidelines for a general risk assessment process (EPA 1976). This process advocated the use of quantitative risk assessment as a means to differentiate risks among chemicals and engineering processes. The guidance was very general, being limited to less than a page within the Federal Register. These guidelines were followed by a paper from the EPA Carcinogen Assessment Group (CAG) (Albert et al. 1977), which provided a strong endorsement of the LNT concept, arguing that linearity was supported by human epidemiological studies (e.g., ionizing radiation and cigarette smoking related lung cancer) and mutagenicity studies that were also claimed to follow a linear dose response and believed to be the underlying mechanisms of carcinogenesis. In a March 15, 1979, Federal Register, the EPA Administrator Douglas Castle stated that "Risk assessment from animal data is performed using the 'one-hit' model" based on the 1976 Interim Guidelines (EPA 1976). He went on to state that "the one-hit model was endorsed by the four agencies in the Interagency Regulatory Liaison Group" based on its highly conservative nature and the uncertainties in extrapolating from animal data to human responses and the possibility that humans may be more susceptible than the animal model, because of broad human interindividual variability in exposures and "other unknown factors". The strongly clarifying and underlying statement of the administrator was due in part to the fact that EPA had used other cancer risk assessment models under other regulatory acts and by other US federal agencies.

According to Albert (1994), Chair of the EPA Cancer Assessment Group (CAG) during the 1970s, the EPA adopted the linear no threshold model (LNT) of the Atomic Energy Commission (AEC) that had been applied to estimating risks from fallout from atomic weapon tests. The LNT model was attractive to EPA since it was very simple to apply; all that was needed in a toxicological sense was to identify the lowest dose of agent that induced a statistically significant response and draw a straight line to the origin of the graph for the dose versus cancer incidence. Its biological plausibility was based on the linearity of mutation dose response within the framework of target theory. He noted that "any difference between chemical carcinogens and ionizing radiation could be waived aside as they both cause genetic damage…"

Statisticians would argue that the straight line extrapolation to zero from the lowest statistically significant response ignored data at the high doses. Thus, during a meeting of leading statisticians called by the CAG, a decision was made to change from the single-hit model to the multi-stage model since it used all the data, while retaining linearity at low dose and being compatible with the concept of cancer being a multi-stage process. Consistent with this assessment, the NAS Safe Drinking Water Committee (1977) recommended the adoption of LNT modeling for risk assessment using a multi-stage model. However, in 1982, the Safe Drinking Water Committee (SDWC) was skeptical about LNT modeling for chemicals and rescinded its endorsement of the LNT model noting "…more confidence could be placed in mathematical models for extrapolation if they incorporated biological characteristics of the animal studies… since the users of this volume will be likely to favor different varieties of the conventional extrapolation models or will have access to some of the newer developmental methodologies, it is premature at this stage to recommend any single approach by selecting it for calculations…" (p 8). However, since LNT modeling was already in use by EPA, in 1983, the SDWC again endorsed the LNT model and its subsequent use became the default methodology for chemical cancer risk assessment. According to Albert (1994), none of the possible models (single hit, multi-hit, logit, probit, multi-stage, others) were biologically credible. The agency simply needed one that would be acceptable. The agency applied LNT risk assessment methods using the multi-stage model for the regulation of trihalomethanes in drinking water in a November 29, 1979, notice in the Federal Register (EPA Environmental Protection Agency (US EPA) 1979a, b), a process that would be followed in subsequent EPA cancer risk assessments.

The parallel, yet converging linear dose–response strategies of the EPA and FDA represent the regulatory origin of current cancer risk assessment practices throughout the world. They are directly traced back to the efforts of Lea (1946) and Timoféeff-Ressovsky et al. (1935), all of which stemmed from the "Proportionality Rule" of Muller (1930).

Eugenics

While the LNT concept for mutation was born within the intellectual and scientific framework of the physics-based radiation target theory, its applications also found supportive resonance within the philosophical, ideological and political frameworks of eugenics. German eugenicists expressed considerable concern that ionizing radiation may hurt the German germ plasm (Proctor 1999; Martius 1931). Educational programs based on these concerns cautioned against exposures to ionizing radiation that might adversely affect future generations of Germans. Recommendations as early as 1927 by the Bavarian Society for Pediatrics and Gynecology stated that women receiving excess X-rays during pregnancy should abort their fetuses. Pushing this concept even further, in 1930, Eugene Fisher, director of the Kaiser Wilhelm Institute for Anthropology, argued that women exposed to X-rays should be permanently prevented from having children (Proctor 1999). Muller's own history is replete with his highly visible association with national and international activities advancing eugenics philosophy and agenda. Even as late as 1955, Muller gave a strong eugenics advocacy presentation in Germany, testing such ideas with a large audience of Nobel Prize winners (The Lindau Mediatheque 1955).

The biophysical concept of the gene had important eugenics implications. Since mutations could be induced by ionizing radiation in a linear at low-dose manner, this concept provided the principal foundation that all ionizing radiation—whether via medical diagnosis/treatment or industrially—was a concern for "genetic health". The genetic toxicology studies of Timoféeff-Ressovsky et al. (1935) transformed these above-cited radiation health concerns, providing biophysical models and the LNT-single-hit model risk assessment paradigm. Such actions provided a key vehicle by which eugenics would focus on radiation protection for preventing the occurrence of genetic defects. In fact, the development and activities of the genetics department of the Kaiser Willheim Institute under the direction of Timoféeff-Ressovsky was affected by such perspectives (Gausemeier 2010).

The concept of LNT for ionizing radiation-induced mutation was, therefore, built upon a scientific/cultural framework and applied to a range of health-related policies, especially those of eugenics during the early decades after the discovery of X-ray-induced mutations. In fact, the eugenics area would serve as an intellectual training ground for how ideas such as LNT could be "softened", humanized and successfully integrated within a post-World War II society. Some aspects of eugenics advocacy and the LNT concept would morph into modern regulatory policy for carcinogen regulation, evolving from that of preserving the gene pool of certain racial subgroups or other targeted populations to a humanistic framework that would reduce mutational risks to entire populations.

Evolution and endogenous mutations

The LNT had its start in an attempt to explain evolution, finding other outlets in the world of eugenics and later public health regulatory policies. While Muller was a leader in these activities, he did not abandon his quest to determine those underlying factors that served to provide the novel mutations for natural selection. In fact, prior to his discovery of X-ray-induced mutations in 1927, Muller reported that temperature increases enhanced the mutation rate by about two-fold (Muller 1928c). However, the temperature hypothesis was placed on the research back burner when high doses of X-rays were found to markedly enhance mutation frequency. Muller would return to the temperature–evolution hypothesis some three decades later, completing an intellectual and professional circle, reflected in the comments of Plough and Ives (1934), his former colleagues at Amherst College (1940–1945) who noted that "since Muller and Mott-Smith conclude that natural radiation is inadequate to account for mutations in nature, it seems possible to suggest that ubiquitous temperature variations may play that role". If Muller had lived into the decades of the 1980s (he died in the 1967), he would have begun to appreciate the so-called other conditions suggested by Oliver (1931) as the cause of the overwhelming proportion of spontaneously occurring mutations is now believed to be derived from endogenous metabolism, for which complex and integrative DNA repair processes have been selected for via natural selection (De Bont and van Larebeke 2004; Lindahl 1996).

Summary

The LNT concept was initially proposed to account for evolutionary change and then later applied for the assessment of risks for some genetic diseases and cancer incidence (Table 2). The initial data upon which the LNT concept was based were limited to a few studies of an acute nature and at very high doses. Within a decade, the LNT dose–response model was provided with a mechanistic foundation via the integration of the single-hit concept within target theory. The LNT-single-hit model was then used by radiation geneticists to frame the intellectual debate on low-dose ionizing radiation risk to the human genome. It provided the basis for the recommendations of the US NAS BEAR I Committee in 1956 for

Table 2 LNT history: the temporal sequence leading to the LNT dose–response model for cancer risk assessment

References	Specific temporal events
Muller (1927)	Mutation findings—X-rays induce mutations in fruit flies ⇓
Olson and Lewis (1928)	LNT model proposed to account for evolutionary changes following Muller's discovery that X-rays can induce mutations in fruit fly germ cells ⇓
Muller (1930)	Develops proportionality rule (i.e., linear dose response) for ionizing radiation-induced mutagenicity ⇓
Timoféeff-Ressovsky et al. (1935)	Application of radiation target theory for mutagens. Used target theory to propose a hit theory for ionizing radiation-induced mutation. The hit mechanism was used to explain the LNT dose response ⇓
BEAR I 1956 (Biological Effects of Atomic Radiation Committee, Genetics Panel)	Proposes the use of the linear dose–response model for germ cell mutation, using the "doubling rule" ⇓
Mantel and Bryan (1961)	Develops carcinogen risk assessment model based on the probit model. This activity was undertaken to advise US governmental agencies on chemical risk assessment ⇓
FDA (1973)	Proposes a probit-based quantitative risk assessment method for cancer risk based on the Mantel and Bryan 1961 paper. The proposal stated that an acceptable risk was 1/100 million ⇓
EPA (1976) (see Albert et al. (1977), Anonymous (1979)	Proposed guidelines for carcinogen risk assessment based on quantitative risk assessment. Recommended a linear dose–response model ⇓
FDA (1977)	FDA rule finalized, retaining the Mantel-Bryan model with some modifications. The acceptable risk value was changed to 1/1 million (10^{-6}) ⇓
U.S. NAS Safe Drinking Water Committee (1977)	Recommended that EPA adopt LNT for carcinogen risk assessment. This recommendation was profoundly significant given the widespread multimedia regulatory functions of EPA. Within 2 years of the recommendation, EPA applied the LNT to the regulations of trihalomethanes (e.g., chloroform) in drinking water ⇓
FDA (1979)	Replaced the modified Mantel-Bryan model with the LNT model for carcinogen risk assessment, based on the following reasons: 1. Linear procedure is least likely to underestimate risk. 2. Linear extrapolation does not require complicated mathematical procedures. 3. No arbitrary slope is needed to carry out linear extrapolation. 4. Several significant limitations were found with the application of the Mantel-Bryan model (Anonymous 1979) ⇓
EPA (1979a, b)	EPA established a national drinking water standard for trihalomethanes (including chloroform) based on an LNT methodology as recommended by the US NAS Safe Drinking Water Committee (1977)

the switch from a threshold to a linear dose–response model for estimating ionizing radiation-induced germ cell mutation using the doubling dose concept. The LNT-single-hit model was soon generalized to the process of cancer risk assessment and adopted by national and international committees concerned with ionizing radiation by the late 1950s and early 1960s. Five years later, Mantel and Bryan (1961), researchers at the US National Cancer Institute, proposed a probit model-based cancer risk assessment method. It was the Mantel and Bryan (1961) model that was proposed by the FDA in 1973 for cancer risk assessment procedures, being replaced with a LNT model by the FDA in 1979, the same year that EPA applied the LNT for the regulation of carcinogens (i.e., trihalomethanes) in drinking water. The LNT model and its single-hit explanation/mechanism theory, therefore, can be traced back to the concept of radiation-induced mutation target theory as proposed by Timoféeff-Ressovsky et al. (1935), which was founded on the proportionality rule of Muller (1930) which itself had its origins in the 1928 paper of Olson and Gilbert that created the LNT concept following the seminal findings of Muller (1927) that ionizing radiation could induce mutation in the germ cells of fruit flies.

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

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