The significance of the failed historical foundation of linear non-threshold model for cancer risk assessment

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Abstract: The linear non-threshold (LNT) single-hit (SH) dose response model for cancer risk assessment is assessed with respect to its historical foundations. This paper examines and summarises how mistakes, ideological biases, and scientific misconduct by key scientists affected the acceptance, validity, and application of the LNT single-hit model for cancer risk assessment. This analysis concludes that the LNT single-hit model was inappropriately adopted for governmental risk assessment, regulatory policy and practices, and for risk communication.

Keywords: dose response; linear dose response; cancer risk assessment; mutation; history of science; threshold dose response; Manhattan Project; National Academy of Sciences.

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Biographical notes: Edward J. Calabrese is a professor of toxicology within the School of Public Health at the University of Massachusetts at Amherst. He has published over 900 articles in the peer-reviewed literature. Over the past 30 years he has investigated in depth the nature of the dose response in the low dose zone, with the overall findings supporting the conclusion that the hormetic-biphasic dose response is fundamental to biology with widespread public health and medical applications. This long-standing interest in hormesis lead him to explore in considerable depth the historical foundations of the LNT dose response model resulting in major new revelations that are summarised in this issue of the journal.

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The LNT model for cancer risk assessment emerged from the firm belief and assertion of the U.S. radiation genetics community of the 1930–1970s period (Calabrese, 2019a). This community built their beliefs on the conclusion of Muller (1927) that the induced transgenerational phenotypic changes in *Drosophila* via the use of high doses of X-rays he produced in his Nobel Prize research were due to gene mutation. Following the subsequent research of two students who showed that X-rays induced similar 'gene' mutations in a linear fashion, but also at very high doses, Muller claimed the existence of the Proportionality Rule, asserting that the dose response for X-ray induced gene mutation was linear down to a single ionisation (Calabrese, 2017c, 2019a). Some five years later a team of prominent physicists and radiation geneticists integrated target theory with Muller's findings, creating the single-hit LNT model, providing a mechanism for the LNT model/Proportionality Rule (Timofeeff-Ressovsky et al., 1935). These actions would culminate in the recommendation of the U.S. National Academy of Sciences, Biological Effects of Atomic Radiation I (NAS BEAR I), Genetics Panel recommendation, some two decades later, of a switch from a threshold dose response to the LNT model based on the radiation geneticist mantra that all induced gene mutations were cumulative, non-repairable, irreversible, and displayed a linear dose response (Anonymous, 1956). This recommendation inspired the National Committee on Radiation Protection and Measurements (NCRPM) (1960) to generalise this recommendation for germ cells to somatic cells two years later, applying it to cancer risk assessment. It was this sequence of events that propelled the LNT cancer risk assessment model into the public health arena, transforming the fields of environmental health, food safety, radiation health, and occupational health.

The 1956 NAS BEAR I Genetics Panel recommendation was embraced by the Biological Effects of Ionising Radiation (BEIR) 1972 Committee, which based their LNT belief on mega-mouse studies of William Russell at Oak Ridge National Laboratory. The BEIR 1972 Committee was officially charged with offering guidance/recommendations to the fledgling United States Environmental Protection Agency (U.S. EPA) which was created in 1970. In 1975, U.S. EPA adopted the U.S. BEIR LNT recommendation, noting that it was based on the research of Russell. The findings of Russell provided a beacon of scientific reliability as it was founded on such a massive amount of data derived from nearly two million mice and had a mechanistic basis (Calabrese, 2017a, 2017b). This scientific foundation of Russell was acknowledged by EPA as critical since the capacity of epidemiological research to clarify the nature of the dose response in the low dose zone is limited, not being able to adequately detect and resolve radiation risks below 100 mSv due to numerous methodological problems, uncertainties and variations in risk factors within human populations.

The 'acceptance' of LNT therefore was based on the findings and intellectual leadership of Muller and the radiation geneticist research community along with a transition to a mammalian model based on the Russell findings. The epidemiological literature was consistent with the LNT model at high doses but could not resolve the central issue of the nature of the dose response at low doses. This has been the LNT cancer risk assessment foundation for the past nearly half century. In fact, the NCRPM (1960) acknowledged that the LNT cancer risk assessment model was not based on a sound scientific foundation in contrast to the assertive position of the BEAR I Genetics Panel (Calabrese, 2019a). The NCRPM (1960) acknowledged that there are unresolved

uncertainties at low dose, basing their LNT recommendation/endorsement on their version of the 'Precautionary Principle'. This uncertainty was also clearly asserted by the BEAR 1960 Genetics and Medical Panels in separate statements. Yet, when the EPA (see Calabrese, 2017b, 2019a) adopted the LNT from the BEIR (1972) committee, the BEIR (1972) report only recounted the unequivocal recommendation of the BEAR I Genetics Panel (1956) (Calabrese, 2019b), ignoring the uncertainty statements of the NCRPM and the two BEAR 1960 Panels.

Thus, the fledgling EPA, without acknowledging the scientific weaknesses of the LNT model, moved forward with bureaucratic certainty, applying the LNT for ionising radiation and chemical carcinogens, giving the public false impressions of precise cancer estimates such as a dose causing a risk of $1/10^6$, that could never be studied nor verified.

Over the past ten years numerous papers have revealed many previously unknown details of the Muller-BEAR I and II and BEIR I era. These revelations have shown that:

- Muller (1927) did not induce gene mutations in his 1927 major paper – but principally modest to mostly massive gene deletions (Calabrese, 2017c).
- The single-hit LNT model was based on the false assumption of gene mutations induced by ionising radiation at high doses (Calabrese, 2017c).
- The Manhattan Project genetics research at the University of Rochester with the leadership of Curt Stern has now been shown to have been presented in a deliberately deceptive manner to support LNT (Calabrese, 2011a, 2012).
- Muller was deceptive in his Nobel Prize lecture, asserting that the threshold concept had no scientific standing and should be replaced by LNT, knowing all the while, that the Caspari and Stern (1948) study at the University of Rochester supported a threshold (Calabrese, 2011b). The new gold standard of BEIR I (1972) that was based on the massive experiments of William Russell was challenged Paul Selby who found major errors some 20 years later in Russell's control group, forcing the Russells to increase its control group mutation value by 120% changing the linear estimate to a threshold response (Calabrese, 2017a, b).

The point of this LNT recapitulation is to raise the philosophical, yet practical question, of what happens to a science hypothesis that becomes the basis for national and international regulation when its scientific basis is no longer reliable? Yet, the scientific culture, all the way from study design, to testing, to biostatistical modelling, to cost-benefit and the overwhelming precautionary principle concerns, were based on false certitudes that created a broad and deep series of societal actions.

The question arises concerning what to think and do when the basis of a fundamental societal scientific belief becomes discredited. How should society continue to think about the issue of cancer risk assessment in light of these current developments? A simple common sense solution, that is, that lower exposure almost always makes sense, is type of personalised precautionary principle. This approach is the equivalent of choosing caution over risk taking. While this may appear to be good advice for members of the general public, what posture should regulatory agencies take? In today's world, such agencies should strive for greater transparency. They should share with the public what these new revelations concerning cancer risk assessment are and mean for regulatory

agencies, the public health, the risk communication message for the media, school systems and the public. To date, regulatory agencies appear to have ignored these scientific developments and have seemingly doubled down on their assertions to support LNT, holding to a belief without a credible history and scientific foundation. While this position may seem to work, in the end, it can't. Why? The challenge will be factual. The EPA adopted the LNT in the mid-1970s, applying it to all sorts of regulations, claiming that 80% of human cancers were related to environment. Now 50 years later, with numerous strict and enforceable standards for carcinogens long in place, such regulations have not affected the tumour incidence (Calabrese, 2019c). Thus, after such a long period of time and with trillions of dollars spent to reduce such risks, the EPA actions have been a dismal public health failure. EPA's predictive models and other methods of assessment have been in serious error. This development calls for a serious re-evaluation of the nature of the cancer risk assessment process, with the goal of deriving regulations that are finally based on sound science and a proper understanding of the cancer causation.

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