Regulation of Carcinogens: What Went Wrong

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Introduction

As a professor of toxicology in the School of Public Health and Health Sciences at the University of Massachusetts, one of the courses that I teach each year is Environmental Risk Assessment. Among the topics covered are the history of environmental legislation, how such legislation created the legal framework to establish environmental exposure standards, and the scientific basis for regulation of chemical carcinogens and ionizing radiation. In that course, we also place these types of regulation in their social, political, economic and international context.

Current regulations are based upon a deliberate misrepresentation of the scientific basis for the dose response for ionizing radiation-induced mutations by the former leaders of the radiation genetics community. These actions culminated in a successful attempt to deceive and manipulate the scientific community and the general public of the U.S and world community by the prestigious U.S. National Academy of Sciences (NAS) Biological Effects of Atomic Radiation Committee (BEAR-I)-Genetics Panel in 1956 when it recommend that the dose response for radiation-induced mutation be changed from a threshold to a linear dose response.

This seemingly minor technical matter can best be shown with a simple illustration (Figure 1). This model, called the "linearity-no dose threshold" (LNT) searches for the lowest exposure to a carcinogen or ionizing radiation that is associated either with substantial mutations or cancer itself. That should be the starting point for any dose-response model, but it is not. Instead, a line is drawn backward from the detection threshold data point to the origin on the graph. The implication is obvious. By forcing the response through the origin, any exposure—including the most minuscule—is claimed to be dangerous.

This switch to a linear dose response by the National Academy misled the world's regulatory community, affecting carcinogen standards for chemicals and ionizing radiation to the present time. Here, we will demonstrate that a small group of ideologically oriented and

prestigious scientists took advantage of their status and opportunities to facilitate a coup d'état concerning carcinogen regulation. Their revolution has been successful for more than half a century, that is, through more than two generations of scientists and the entire modern regulatory history, predating Environmental Protection Agency (EPA), Occupational Safety and Health Administration (OSHA), National Institute for Occupational Safety and Health (NIOSH), Agency for Toxic Substances and Disease Registry (ATSDR), and influential professional societies, including the Society of Toxicology (SOT), the Society for Risk Analysis (SRA), and many others. We will further demonstrate that the science behind this coup was known to be false at the time it was undertaken. The LNT model became accepted as truth and uncritically incorporated into environmental toxicology and risk assessment history, becoming unquestioned dogma and a core scientific belief. It is passed on to new generations of toxicologists, regulators, policy makers and the general public as our scientific and regulatory culture.

While the situation described above is bad enough for the LNT, the regulatory community also adopted the threshold dose response model for non-carcinogens, assuming that it would make accurate predictions of responses in the low dose zone. However, no person or group within the entire regulatory edifice of multiple federal and state agencies in any country ever validated the capacity of this model to make accurate predictions in the low dose zone. Regulatory actions would be highly dependent upon this model to protect the public health. Some 70 years later, when such vetting of the regulatory dose response models finally took

place, the threshold dose response model (as well as the linearity dose response model) was an abject failure.[1,2,3,4,5]

The next section of this chapter will supply the supporting facts. A further issue is that global regulatory agencies, as well as many in the scientific community, are not aware that the risk assessment regulatory framework is built upon a series of misrepresentations, unexamined assumptions and erroneous beliefs that will later be seen as complex social constructs, including an intriguing combination of self-interest and transgenerational inheritance of unquestioned concepts. It will become obvious that regulatory scientists and administrators benefitted from the existing LNT paradigm—so much so that they didn't do the simple falsification experiments that are at the core of science.

In the first decade of the 21th century I became interested in subjecting the hormetic dose response to a series of validation tests using a number of different data sets. However, since I had never attempted to validate a dose response model, I first needed to determine how the scientific and regulatory communities had validated the threshold dose response model. After several months of active searching for articles and any related material concerning the validation of the

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[1] Calabrese EJ, and LA Baldwin, (2001). The frequency of U-shaped dose-responses in the toxicological literature. *Toxicol. Sci.* **62**:330-338.

[2] Calabrese EJ, and LA Baldwin. (2003). The hormetic dose-response model is more common than the threshold model in toxicology. *Toxicol. Sci.* **71**:246-250.

[3] Calabrese EJ, et al., (2006). Hormesis outperforms threshold model in National Cancer Institute antitumor drug screening database. *Toxicological Sciences* **94**(2):368-378.

[4] Calabrese EJ, et al., (2008). Hormesis predicts low-dose-responses better than threshold models. *Int. J. Toxicol.* **27**:369-378.

[5] Calabrese EJ, et al., (2010). Hormesis in high-throughput screening of antibacterial compounds in *E. coli. Hum. Exp. Toxicol.* **29**:667-677.

threshold dose response model, I began to wonder if it had ever been done. I then called a number of senior toxicologists both in and out of government asking if they could direct me toward the validation studies. None could. I then re-devoted my efforts trying new search strategies to uncover such validation studies, yet none were successful. I then decided to include mentioning of these failed attempts in seminars and other presentations hoping to inspire someone in these scientific audiences to come forward with information on such validation. No one ever did. At some point, approaching two years into this search effort I came to the conclusion that the threshold dose response model had probably never been validated during the entire 20th century. This leads me to conclude further that entire national standard setting programs were in fact built upon an assumption rather than a reality. It was instead a paradigm of scientific correctness that had been passed down from one generation of scientists and regulators to another, codified into textbooks, legislation and hazard assessment protocols for all chemicals and drugs. It is truly mind boggling that no one ever challenged it.

Having never discovered any prior effort to validate the threshold dose response model my colleagues and I set forth to do so with multiple independent data sets. The broader intention was to test the capacity of the threshold, linear and hormetic models to make accurate predictions in the low dose area. These efforts, which resulted in the publication of several papers in leading toxicological journals, revealed that both the threshold and linear dose response models consistently and uniformly poorly predicted responses in the low dose zone (Calabrese et al., 2008, 2010; Calabrese and Baldwin 2001, 2003). In fact, their respective performances were far below any fair minded acceptable level. The only dose response model that performed consistently very well in each of the evaluations was the hormetic or biphasic dose response model. Ironically, it was the model first proposed by Hugo Schulz more than a century earlier

and the one that was rejected and marginalized by the medical and scientific communities that actually passed these series of tests. These results were as striking and consistent as they were important. The findings revealed that the threshold dose response which became the only model of choice by the medical, scientific and regulatory communities starting the late 1920s for chemicals and radiation exposures was shown to have very significant limitations. In addition, my concurrent research on the hormetic dose response had already revealed many thousands of cases in which the threshold dose response model also failed to predict responses in the low dose zone (Calabrese and Blain, 2011).

What we had found was that the entire regulatory edifice for chemical and radiation had been built upon a failure of the scientific, medical and regulatory communities to ever take the time to vet the model that they were betting the health of the human population upon.

The analogy between the fiasco of government dietary advice and regulatory science is painfully obvious. One caused an epidemic of obesity and type II diabetes, and the other caused countless morbidity by "outlawing" things that would be beneficial in small doses. The fact that the analogy between the therapeutic model and the hormetic response is testimony to the power of paradigm protection.

Assuming that one intellectual generation lasts about twenty years, then we have now passed through four to five generations of physicians/scientists who accept the threshold model as literally an act of faith. We have been using an alternative model that performed far below the one that their scientific and medical ancestors had rejected.

A serious problem with this situation is that the scientific, medical and regulatory communities had every professional incentive to protect the existing paradigm. The biphasic dose response would be easily marginalized by continuing to associate it with the high dilutionist wing of the homeopathy party, an easily ridiculed group. This strategy worked in the day of Professor Alfred Clark, and it works today (Calabrese, 2005) and the strategy was a good one, even if false. However, oft-repeated falsehoods become truths. Biphasic dose responses would not be seen often and when they were seen they would be trivialized and discounted. We are still in the early stages of Thomas Kuhn's model for paradigmatic change, mentioned early in this volume:

> "In science…novelty emerges only with difficulty, manifested by resistance, against a background provided by expectations. Initially, only the anticipated and usual are experienced even under circumstances where the anomaly is later to be observed."

We are now at the stage where only a very few are "observing the anomaly", in no small part because there is very little incentive and a lot of professional downside in doing so. When this lasts for multiple scientific generations an alternative, more explanatory paradigm is systematically suppressed. The modern scientific, medical and regulatory communities have been victimized by a war fought a century ago. Scientists often do not place a high priority on history. This is seen in the low numbers of citations of excellent papers in history of science and medicine journals. Too few take the time to ferret out the past and its current impact.

Linear-No-Threshold: Origin and Implications

Ultimately the threshold model would morph into the linear-no-threshold model (LNT), one in which a threshold still existed, but it was at first exposure or ingestion of any magnitude, obvious at great variance with the biphasic dose response (hormetic) model. The nonzero threshold model was promoted by the radiation genetics research community. It was an outgrowth of the novel 1927 research findings of Hermann J. Muller that very high doses of x-rays could cause mutations in the mature spermatozoa of the male fruit fly, a discovery that took nearly two decades of intense focus and with much competition (Muller, 1927).

The first challenge to the threshold concept by the mainstream scientific community was offered by two physical chemists from the University of California at Berkeley, one of whom was the internationally famous Gilbert Lewis who would be nominated for the Nobel Prize some 32 times before dying in 1946 from cyanide poisoning in his laboratory. These two chemists were not part of the allopathic medicine and homeopathy feud, but scientists who were seeking a mechanistic understanding for the process of evolution, one of the most significant questions of that time period (Olson and Lewis, 1928).

In the aftermath of Charles Darwin and Gregor Mendel there was great interest in trying to discover the mechanism by which evolution occurred. It was believed that evolutionary change must be mediated via gene mutation. The problem was that since about 1910 and for the next 17 years no one had been successful in inducing mutations via a whole host of toxic agents as well as via the use of different types of radiation. With Muller's breakthrough Gilbert proposed that the mechanism of evolution was mutation caused by cosmic rays and background terrestrial radiation. Because this dose is so small, he had to assume that the dose response would have to be linear at low dose. As a result, Gilbert's hypothesis was only able to account for about

1,300th of the background mutation rate, based on Muller's fruit fly data and assuming a linear dose response relationship (Muller and Mott-Smith, 1930). While Muller retained his commitment to understand the causes of evolution it seemed pretty clear that the mechanism would not be found in the Gilbert background radiation hypothesis.

While Muller did not support the arguments of Gilbert for cosmic and terrestrial radiation as being the driving force for evolution, he soon directed several students to assess the dose response features of the X-ray treatment. *Muller's Nobel Prize research did not yield a linear dose response.* Of his three experiments, the third lacked a control group thereby preventing a firm assessment, the second gave the suggestion the responses varied non-linearly with dose but with the square root of the dose while the initial experiment yielded data consistent with a threshold dose response (Muller 1928).

The student research continued to employ what amounted to very high doses. Nonetheless, these researchers reported linear dose responses. Based on these findings Muller developed a very strong belief that the dose response was linear and that linearity would extend down to a single photon (Oliver, 1930, 1931; Hanson and Heys, 1929, 1930). The lowest doses tested in their linearity-supporting articles were about 300,000-fold greater than background. Furthermore, Muller was selective in what data he chose to focus on as there were other contemporary credible findings displaying a threshold perspective (Patterson, 1928; Weinstein, 1928; Stadler, 1930, 1931). In fact, on balance there was more support for a threshold dose response model interpretation rather than a linear perspective. Yet, Muller would give the impression that he passionately and firmly believed in the reality of the dose response for mutation being linear in the low dose zone. It is difficult to understand how Muller would make a

"commitment" to a dose response model for low dose predictions when there was no testing in the low dose zone!

Despite the use of extremely high doses and that other data challenged a linear perspective Muller would nonetheless introduce the term "Proportionality Rule" in 1930 to define the nature of the dose response for ionizing radiation induced mutation in the low dose zone (Muller, 1930). He was claiming that ionizing radiation and mutation were different than other agents and endpoints, respectively. He claimed that radiation-induced mutations do not show a threshold but act in a linear fashion. Soon thereafter the term Proportionality Rule gained traction within the radiation geneticist community. It gained such a standing in large part due to the fact that Muller had become famous, being the first to induce changes in heritable material.

The Manhattan Project and the LNT

The Roosevelt Administration created the Manhattan Project in response to Albert Einstein's 1939 letter to President Roosevelt on the likelihood of a German effort to build an atomic bomb.[6] As part of this effort, research was undertaken to better assess the nature of the dose response to ionizing radiation. The key research on mutation was to take place at the University of Rochester under the direction of Dr. Donald Charles for mouse studies, and Dr. Curt Stern for fruit fly investigations.

[6] See Chapter 2 of this volume

In the case of the mouse work under Charles, no detailed papers were ever published. Only two brief summaries appeared, one in 1950 and the other in 1961. It is not clear why the mouse work did not yield the type of productivity and insights expected, despite the use of nearly 400,000 animals. Life did not end well for Dr. Charles as he left his position at Rochester and in 1955 committed suicide in a Manhattan hotel, leaving a despondent letter reflecting both job and marriage failings.

On the other hand, Stern's research would revolutionize the field of cancer risk assessment and eventually lead to the institutionalization of the LNT.

Stern was a towering giant in genetics, having discovered a component of chromosomal crossing-over, a mechanism that is a key foundation of modern genetics. Soon after he began on the Manhattan Project he appointed Muller as a formal consultant. Muller and Stern were of the firm belief that the experiments with the fruit fly model would provide strong support for the LNT model, confirming their long-held beliefs. Their efforts would be important to the field of radiation genetics as it would be the most extensive effort to date.

Furthermore, they would be working with highly experienced individuals. In their first major experiment under the direction of Warren Spencer, an Ohio State University Ph.D. graduate and a fruit fly expert on leave from the College of Wooster in Ohio, they found that acute doses (i.e., total dose given over 2-40 minutes) of X-rays appeared to cause a linear dose response relationship for germ cell mutations. This research, which became highly acclaimed, had many important methodological limitations, especially affecting the validity of low dose responses (Calabrese, 2011b). Yet, such limitations were either ignored or missed by experts in

the field. A detailed internal letter by Muller in 1947 assessing the Spencer research also failed to identify any of the many now recognized weaknesses of this research (see Calabrese, 2011b).

A follow-up study by Ernst Caspari, was designed to assess the effects of gamma rays that were administered throughout the entire life of the fruit fly, providing chronic exposure. The comparative dose rate in the Caspari experiment was about 1/13,000th of the lowest dose given by Spencer. Even though both studies administered the same total dose, Spencer delivered it in a few minutes, while it took three weeks in the Caspari study. According to the LNT model, both studies should have resulted in the same amount of damage since ionizing radiation was assumed to cause damage that was cumulative and irreversible (Calabrese, 2011b, 2013a,b).

It did not. To the surprise of Caspari, the mutational data was not cumulative, revealing an apparent threshold response. In effect, the data of Caspari challenged the assumption that mutation damage was best predicted by total dose—a key feature of the LNT model—rather than by dose rate. Stern initially would not accept these findings, claiming that the data were most likely an artifact of the experiment with the control group displaying a much higher than normal response, thereby leading to the threshold, rather than the linear dose response. Caspari dug in, searched the literature, and found a number of papers which supported his position that the control group had responded normally, forcing Stern to back down.....at least temporarily (Calabrese 2011a,b; 2013a,b).

While Stern was forced to retreat on the issue of the control group he intervened with a more powerful strategy that would have the same effect, a way to not accept the threshold dose response. He forced the discussion of the Caspari paper to conclude that it was not possible to accept the threshold interpretation until it was determined why this study obtained differing

results than the earlier Spencer work. Stern knew that the two studies had at least 25 significant methodological differences, making them virtually impossible to properly compare. For example, the studies differed in the type of radiation used, the diets the flies were reared on, which sex was exposed to the radiation, the temperature of the study and many other factors. To actually figure out why the two studies differed would be a major undertaking by itself, a task that was never attempted by any of the original researchers, none of Stern's or Muller's subsequent students, nor anyone else since (Calabrese 2011a,b; 2013a,b).

Stern sent this draft manuscript to Muller for review just prior to his travel to Stockholm to receive the Nobel Prize in December of 1946. On November 12, 1946 Muller wrote to Stern telling him that he was shocked by the findings that the data offered a strong challenge to the LNT concept, that the studies needed to be replicated as soon as possible. Yet, he could not criticize Caspari for he was a competent investigator.

Muller would travel to Sweden, and received his honor. Despite just having read Stern's paper, in his Nobel Prize Lecture he stated that it was no longer possible to even consider the possibility of a threshold dose response for ionizing radiation. The risk assessment field had to switch from using the threshold dose response model to the LNT model. He made these comments after having just seen the most extensive set of data on the topic, from a research team that was considered very experienced, where Muller himself provided his own Muller-5 fruit fly strain and where he was a very involved consultant. Detailed letters between Muller and the Rochester team document the extensive role that Muller had in helping to shape their research strategies, study design and research methods (Calabrese, 2012).

When Stern did publish his findings, all five experiments (i.e., the Spencer, Caspari and Uphoff research) were summarized in a table of a one page technical note in the journal *Science* (Uphoff and Stern, 1949). Since much data were missing and no methods were presented he stated that a follow up detailed paper would be published with all the necessary methods and data. However, in a significant failing, Stern never published the follow up paper as promised.

It is more than curious that *Science* would have published such a note without any supportive material, suggesting that Stern may have used a personal contact at *Science* to get his paper published. Several months prior to the submittal of their manuscript, Bentley Glass, the first Ph.D. student of Muller at the University of Texas, who had received a Fullbright Fellowship to work with Stern, become an Editor at *Science*. Given the expertise of Glass in fruit fly mutation it is hard to imagine that he was not involved in some oversight of the Uphoff and Stern manuscript (Calabrese, 2013a,b).[7]

This was not the first time that *Science* would give research related to Muller a strong push forward. For example, when Muller (1927) published his Nobel Prize securing paper in *Science* it did not contain any data. All his paper provided was a detailed discussion of the findings. How was this possible? It seems that Muller knew he was in a race to be the first to show that mutations could be artificially induced. The only way he could assure winning the race was to put the cart before the horse and present only the discussion. Without such deferential treatment from *Science*, he may have come in second as others such as Stadler from the University of Missouri were not far behind.

[7] The November, 2009 "climategate" emails demonstrated similar editorial hanky-panky in climate change research. No one, however, has ever done a systematic and scholarly analysis of editorial tampering.

At a critical time in environmental public health history, the National Academy of Sciences convened a major assessment on the public health implications of low doses of radiation, including their mutational effects. Concerns with public exposure to ionizing radiation were heightened during the early 1950s as the U.S. and the Soviet Union were in an arms race and were actively testing their atomic weapons with above ground testing. Despite their low exposures, radionuclides quickly achieved worldwide distribution, finding their way into foods and drinking water. Exposure to ionizing radiation was being rapidly expanded from that of patients and medical personnel to a public health concern.

Until this time Muller and his group of radiation geneticists had always been out voted and/or out maneuvered on the issue of the nature of the dose response, that is, the threshold versus linearity debate. Now the genetics panel of the NAS committee had the votes to switch the risk assessment paradigm. Finally, they had their chance to protect the human genome from radiation induced mutation and the occurrence of heritable diseases as well as cancers. In fact, the radiation geneticist community of that era deeply believed that it was their responsibility to save future generations from genetic harm. No other discipline had their knowledge, experience and unique insights. This was not only their time but also their opportunity to change risk assessment policy in the U.S. and worldwide.

For two decades the radiation genetics community had fought to change the risk assessment paradigm for ionizing radiation. They wanted it based on heritable changes and they wanted the dominating threshold model that pervaded the medical community replaced with the LNT model, which was born with the research of Muller with mature fruit fly spermatozoa and

transformed into a mechanism risk assessment vehicle based on the assumption that a single hit could both induce a mutation, possibly leading to birth defects and/or cancer in humans (Timofeeff-Ressovsky et al., 1935).

The National Academy of Sciences BEAR I Committee: How it Misled the World on Risk Assessment

One would have thought that there would have been a major debate on whether the LNT model should replace the threshold dose response for mutation and cancer in this historic convening of the NAS Committee in 1955-1956. It would be a test of the wills, the historically powerful medical community versus the upstart radiation geneticists lead by their Nobel Prize winner Hermann Muller. At least that is how I had thought the series of meetings of these two groups of scientific and medical leaders would go. I obtained the transcripts of their meetings, anxious to read the debate, and to learn what arguments would be the most persuasive and who would lead the way.

To my surprise, there was no debate on this most crucial area. In fact, it became quite clear that a decision had been made prior to the convening of this Genetics Panel that LNT was in and threshold was out, an observation later confirmed in the historical writings of Jim Crow[8] (1995), the last member of this Genetics Panel to die. All that was needed was to stack the Panel with the correct people and the votes would be there. The Genetics Panel was highly leveraged to

[8] In fact, I was fortunate to have shared with the 95 year old Dr. Crow my allegations of Muller's Nobel Prize lecture and other deceptions in a series of e-mail exchanges in the months leading up to his death (January 4, 2012). My first e-mail to him was during the halftime of the Superbowl with his answer arriving before the kick off of the second half!

support the Muller perspective. No time was wasted in this Panel over whether it was LNT or threshold. They simply adopted an LNT perspective and then moved on to other issues.

During the process of their assessment, the BEAR I Genetics Panel would falsify and fabricate the research record concerning the estimate of radiation-induced genomic risk, committing scientific misconduct at the highest possible levels. This has been documented in detail by Calabrese (2015, 2016). It made a decision not to share the profound degree of uncertainty amongst the Panel members but rather, to misrepresent it by removing and changing data concerning estimates of genetic mutations in the U.S. population at a certain level of radiation exposure.

They were quite concerned that the scientific community, governmental officials and the general public would not accept their radiation health/risk policy recommendations, including the adoption of LNT for risk assessment, if they were honest and shared the sizable uncertainties. They deliberately misrepresented the research record in their formal Panel publication in the journal *Science*. Further covering up of their actions occurred when a group of prominent biologists requested that the Panel provide the documentation for their policy recommendations and they voted not to provide this, a vote that was shared with the President of the NAS, Detlev Bronk, thus linking the deceptive practice right to the top. All such actions of the Panel are documented in the historical record (Calabrese 2015, 2016).

This set of coordinated deceptions was used to persuade other scientific bodies and the international community to follow their leadership and directions. Yet, this course of action was surprisingly easy. It started with the activism and leadership of the Rockefeller Foundation, which provided the funding for the panel in the first place, printing many thousands of copies of

the deceptive report and distributing it widely, including all public libraries in the country. It was also soon arranged to have the journal *Science* lend its immense credibility to the dose response switch by permitting the Panel to publish a substantial paper on their conclusions (BEAR I, 1956). Congressional hearings were also convened and members of the panel testified, advocating the use of the LNT, and basing it largely on the publications of Stern and his colleagues, Spencer, and Uphoff (Calabrese, 2013a,b). *Science* journal would play a further role in the process by publishing a profoundly influential paper by the future Nobel Prize winner Ed Lewis (1957) on cancer and radiation exposure, a paper which was heavily dependent upon the Uphoff and Stern technical note. This article obtained a further boost from *Science* once again, receiving a ringing endorsement in an accompanying statement by the Editor-in-Chief of *Science* (DuShane, 1957).

As noted in an oral history, Lauriston Taylor, Chairman of the National Committee for the Radiation Protection and Measurement (NCRPM), stated that other national and international radiation committees, including his NCRPM, were quietly waiting for the proclamations of the U.S. NAS committee as it carried substantial authority. Once their report was made public, these committees soon recommended the switch to the LNT and its generalization to somatic cells so that the LNT could be applied not only to mutational events but also to the issue of cancer risk assessment. Further speeding up the process was the fact that some members of the NAS Genetics Panel served on several of those other panels, thus, extending their impact and influence. In effect, these radiation scientists got to vote two or three times, a further stacking of the deck, and getting multiple bites at the apple.

Within a very short time, the radiation geneticists had lead a profound environmental/medical policy revolution. They got the U.S. government and the world governmental community to adopt a new risk assessment paradigm, even if it was a little short on real data.

There was now a global consensus that there was no safe exposure to ionizing radiation, that the dose response was linear. Even if one could not measure the impact scientifically, it was assumed that even a single ionization would cause permanent damage and enhance the risk of genetic damage and cancer.

From 1955 to the end of the decade that the most significant changes in environmental policy occurred. Not long after the publicity associated with the linearity recommendation of the BEAR I Genetics Panel its impact began to be seen in the scientific literature as Newell (1957) applied LNT to population based mutation frequency while Buck (1959), Grendon (1965) and others applied the LNT concept to cancer risk assessment. This Panel's actions also profoundly ramped up fear of the continuing arms race and probably influenced the U.S. and Soviet Union to end above ground testing. The adoption of the LNT was also at the heart of the creation of something called the Precautionary Principle, a highly conservative way of thinking about risks from emerging technologies, chemicals and radiation.

There was a major problem with all the success of the BEAR I committee, and that of the radiation geneticists. The science upon which they based their good intentions of saving the world was known by the leadership to be in error. In retrospect, the Genetics Panel of the BEAR I Committee failed to vet the principal research findings upon which their recommendation to switch from a threshold dose response model to the LNT was based. The committee had simply

come under the leadership spell of Muller and his longtime and unrelenting advocacy of the LNT. For Muller, his 25 year crusade was finally realized.

While it may be possible to see this band of radiation geneticists as misguided in their romantic heroism to save world from genetic harm due to nuclear testing and the excessive use of medical X-rays, information is also available in the preserved private correspondence of some of the members of the BEAR I Genetics Panel to suggest that professional self-interest may well have been a comingled prime motivator in their fight to "ban the bomb". The majority of the Genetics Panel were active researchers in university settings. Just as is the case today, there was a publish or perish mentality. Research dollars were critical and such resources were provided by governmental organizations and foundations for these investigators. Essentially all of the academic members of the Genetics Panel were externally funded. While competition for funding was therefore central to the process, letters indicated that some members of the BEAR I Genetics Panel also acted to deliberately overstate the nature of the radiation dangers to the public health and to use highly inflammatory language in order to make their area of research more frightening and important, that is, more fundable. By advocating strongly for the LNT the members of the Genetics Panel would make their area of paramount importance, enhance their professional opportunities for key governmental advisory committees, research funding, and consulting activities.

Muller, BEAR I and EPA Cancer Risk Assessment: The Connection

The recommendations of the BEAR I Genetics Panel proved to be of profound significance for the cancer risk assessment of ionizing radiation (Calabrese, 2009b). However, it did not stop there. The recommendation of the Panel had a long reach as it spread across decades, agencies and agents. Although intended for ionizing radiation, the concept of LNT was general and once it could be reliably shown that chemical carcinogens were often mutagens it would not take too long for the newly emerging EPA to make the BEAR I dose response recommendation their own. In his writing of the history of carcinogen assessment, Roy Albert (1994), the chairman of the EPA Cancer Assessment Group (CAG) stated that during the 1970s the EPA adopted the LNT of the AEC that had been applied to exposures from fallout from atomic weapon tests. He noted that the LNT model was simple and its simplicity made it attractive to the EPA. In fact, all that was needed was to identify the lowest dose of an agent that induced a statistically significant response and draw a straight line to the origin of the graph for the cancer incidence. The biological plausibility was based on the linearity of the mutation dose response as set within the framework of target theory. Importantly, Albert noted that "any difference between chemical carcinogens and ionizing radiation could be ignored as they both caused genetic damage..". The actions of EPA to adopt the recommendations of the BEAR I Genetics Panel for its cancer risk assessment activities reveals that the foundation of modern cancer risk assessment in the U.S. and in most countries was based on the deceptions of Muller and Stern and the manipulation by the NAS.

Of considerable importance is that Muller's research, as well as that of Stern during the Manhattan Project period were performed with mature spermatozoa. Muller, Stern, the Drosophila-dominated radiation genetics community and advisory committees around the world, extrapolated findings from mature spermatozoa to somatic cells, not realizing that mature

spermatozoa lacked the capacity to repair damaged DNA. It was this lack of DNA repair within the mature spermatozoa that lead to its heightened mutational susceptibility and its capacity to grossly over estimate mutational risks in other reproductive and somatic cells.

This was especially the case at low dose-rates, and created a belief among the radiation geneticists in the correctness of the LNT model. This belief, which was initiated by the BEAR I Committee Genetics Panel and soon generalized to cancer risk assessment by other advisory groups, was a flaw of major proportions. This action was something like using mutating bacteria lacking DNA repair to estimate genetic risks in humans. Not only did this group of radiation geneticists create public policy by deception, they also got the science wrong.

The concept of dose rate in radiation would be unequivocally reported in 1958 by William Russell and DNA repair a few years later. However, the environmental die was cast in 1956 by the BEAR I Genetics Panel that lead to the codification of LNT in the regulatory process with its protection ensured by the adoption of a guiding Precautionary Principle, preventing regulatory "science" from being self-correcting as new scientific understandings emerged.

Final Thoughts

At its core the process of risk assessment for carcinogens and non-carcinogens in the U.S. is based on fraud, incompetence and ideology at the highest levels of government. In its now more than four decades in which the U.S. EPA has blindly accepted dose response frameworks for the assessment of risks that were fabricated in the case of mutagens/carcinogens and never validated in the case of non-carcinogens. The agency built their entire regulatory edifice upon

models that have been shown to not accurately predict the risks of toxic substances in the low dose zone, the location where humans spend the vast majority of their time.

It is hard to imagine that the regulatory agencies and all the regulated industries and their subsidiary consultants never thought to examine the foundations upon which all the regulations that they debate, fight and litigate are based. The failure of the scientific community and the regulatory agencies to discover the deceptive and scientifically incorrect origins of the LNT and how it came to impact the risk assessment process is important as this severely impacted the development of environmental legislation, the basis of health standards in air, water, food, soil, and the health of the population, the economy, the proper use of natural resources, and the course of environmental and public health history. Correcting this error remains a fundamental challenge to, and a necessity for the regulatory community.

Acknowledgement

Long-term research activities in the area of dose response have been supported by awards from the US Air Force (FA9550-13-1-0047) and ExxonMobil Foundation over a number of years. The U.S. Government is authorized to reproduce and distribute for governmental purposes notwithstanding any copyright notation thereon. The views and conclusions contained herein are those of the author and should not be interpreted as necessarily representing policies or endorsement, either expressed or implied. Sponsors had no involvement in study design, collection, analysis, interpretation, writing and decision to submit.

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Figure 1. Comparison of the three leading toxicologically-based dose response models (threshold, linear, and hormetic) used in risk assessment