US Risk Assessment Policy: A History of Deception

A Response to Arden Rowell, *Allocating Pollution*, 79 U Chi L Rev 985 (2012)

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INTRODUCTION

Strategies to limit the general public's exposure to toxic substances—via national standards such as community-based drinking water and air quality standards, food residue regulations, hazardous-waste siting decisions, or other strategies—are based on multiple factors including social, political, cultural, historical, economic, technological, as well as public health–related concerns. At the core of these decisions is the need for risk assessment estimates to be based on a sound foundation, using scientifically validated procedures and having high reliability. However, while it may be hard to believe, and even more difficult to accept, the foundation of our fundamental dose-response model—that is, the threshold dose-response—upon which all public health standards were originally based, and upon which we still highly depend, was never validated by the regulatory and scientific communities prior to its adoption by the FDA, EPA, OSHA, and other agencies in the United States and elsewhere in the world.

I. THE HOMEOPATHY–TRADITIONAL MEDICINE CONFLICT

This "little" oversight by our regulatory agencies should be seen as what it is—a profoundly scandalous failure and a mistake never corrected once identified. How could the regulatory and scientific communities have gotten the most fundamental pillar of their discipline wrong, never corrected the error, and then built an entire regulatory edifice upon it?

The basis of this fundamental error occurred well before there was an EPA, OSHA, or even an FDA.[1] The original dose-response error emerged

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[1] See generally E.J. Calabrese, *Historical Blunders: How Toxicology Got the Dose-Response Relationship Half Right*, 51 Cellular & Molecular Bio 643 (2005) (discussing the error made by the toxicology field because of its rejection of the hormesis concept). See also Edward J. Calabrese, *Toxicology Rewrites its History and Rethinks its Future: Giving Equal Focus to Both Harmful and Beneficial Effects*, 30 Envir Toxicology & Chemistry 2658, 2660 (2011) (explaining how the homeopathic, biphasic dose-response was discredited by mainstream allopathic practitioners upon its introduction in

out of a long-standing and profound dispute between what we now call traditional medicine and homeopathy. While traditional medicine crushed homeopathy in the early decades of the twentieth century, profoundly reducing its influence throughout the remainder of the twentieth century, this was not the case some 130 years ago, as the two entities battled for power, influence, and market share of the developing health care industry. In fact, homeopathy attracted many patients from the traditional medical camp solely on the basis that its very low-dose treatments posed essentially no risks (even if no benefits) as compared to the often brutalizing treatments of traditional medicine, including massive blood-drawing and the use of highly toxic agents such as mercury in medical treatments.[2]

The issue of dose response and its role in drug discovery in a modern sense arose out of the actions of the traditional physician and professor of pharmacology and toxicology, Hugo Schulz, from the University of Greiswald in Northern Germany.[3] In the early 1880s, Schulz undertook one of the earliest and most systematic, dose-time response–relationship studies while assessing the effects of chemical disinfectants on yeast.[4] What he observed surprised him. That is, at low doses a broad range of agents stimulated the metabolism of the yeast while being toxic at high doses. Schulz was quite surprised and therefore spent considerable time doing extra replications trying to figure out what he must have done wrong for the findings to have come out as they did. After exhaustive rechecking and replications, Schulz became convinced that his results were real and reproducible, even if still surprising and inexplicable. He soon presented

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the mid-1880s); Dr. Bert J. Vos, et al, *Oral History of the U.S. Food and Drug Administration: Pharmacology—Transcription of Recording of Meeting to Discuss the History of Pharmacology in the Food and Drug Administration* 19–23 (FDA June 20, 1980), online at http://www.fda.gov/downloads/AboutFDA/WhatWeDo/History/OralHistories/SelectedOralHistoryTranscripts/UCM265869.pdf (visited Jan 7, 2013) (addressing the FDA's development of toxicological testing methods in the early twentieth century and the contributions of Dr. Chester Bliss to those efforts).

There is no evidence that any US regulatory agency ever funded research to validate the threshold dose-response. The creation of a toxicological framework within US regulatory agencies first occurred within the FDA. The FDA hired Dr. Bliss as a consultant. The so-called father of American biostatistics had worked with Professor Alfred J. Clark of Edinburgh University during the mid-1930s and tirelessly worked to help establish the threshold dose-response model across biological disciplines. Clark is seen as the intellectual leader who suppressed the growth of homeopathy and marginalized Hugo Schulz and his biphasic (hormetic) dose-response. See Calabrese, 30 Envir Toxicology & Chemistry at 2662–63. See also Vos, et al, *Oral History* at 18–19 (cited in note 1).

2 See Irvine Loudon, *A Brief History of Homeopathy*, 99 J Royal Society Med 607, 608–09 (2006). See also Calabrese, *Historical Blunders* at 644–47 (cited in note 1).

3 See Hugo Schulz, *NIH-98-134: Contemporary Medicine as Presented by Its Practitioners Themselves, Leipzig, 1923:217-250*, 1 Nonlinearity in Bio, Toxicology, & Med 295, 301–06 (2003) (Ted Crump, trans) (translated and republished autobiographical statement of Schulz).

4 See generally Hugo Schulz, *Zur Lehre von der Arzneiwirkung*, 108 Archiv für pathologische Anatomie und Physiologie und für klinische Medicin 423 (1887); Hugo Schulz, *Über Hefegifte*, 42 Pflüger's Archiv für die gesamte Physiologie des Menschen und der Thiere 517 (1888).

the interesting experimental findings at a local medical conference. Yet, nothing much was made of the observations.

Things changed about a year later in 1885. It was at this time that Schulz came to place his results in a biological/medical context. Following conversations with his colleague Rudolf Arndt, Schulz came to believe that he had discovered the explanatory principle of homeopathy. He asserted that homeopathic drugs acted at low doses to enhance the adaptive capacity of the body to resist various types of chemical and biological stresses while at higher doses they induced toxicity. Schulz soon became ostracized from the traditional medicine fraternity and became the object of profound professional criticism.[5] At the same time Schulz never embraced the high-dilutional philosophy of Samuel Hahnemann, the founder of homeopathy.[6] In other words, Schulz was very independent minded, following his own scientific path. Nonetheless, Schulz handed homeopathy the first formal dose-response relationship; that is the biphasic dose-response, which he called the Arndt-Schulz Law, giving credit to his friend and colleague. This was a key turning point in the history of medicine and public health. It became important because the medical community was "scooped" by homeopathy concerning the dose response. In fact, the medical community could not accept even the possibility that the biphasic dose-response might have value since it was now a central tenet of the "enemy" homeopathy.

Over the next five decades of his professional life, Schulz became further marginalized as homeopathy saw its fortunes toppled by its own inherent weaknesses and the impressive rise of its opposition. Despite the fact that homeopathy was losing the battle with traditional medicine, it did not mean that its dose-response model was wrong or of little general medical value. Yet, this model was shunned by the intellectual leaders of modern medicine, who subsequently came forth with their own model, the threshold dose-response. This soon became the model of the scientific and medical communities, with sophisticated statistical packages dressing it up and enhancing its credibility and applications. The threshold model provided the foundation for hazard assessment, study designs, sample sizes, and all those factors that would serve the risk assessment process for agencies like EPA.[7]

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[5] See generally P. Wels, *Das Lebenswerk von Hugo Schulz*, 170 Naunyn-Schmiedebergs Archiv für Experimentelle Pathologie und Pharmakologie 744 (1933). This article was based on a eulogy for Schulz following his death in 1932.

[6] Horst Böhme, *Hugo Schulz (6.8.1853 –13.7.1932): Sein Leben und Werk* (Freien Universität Berlin 1986).

[7] See Edward J. Calabrese, *Methodological Approaches to Deriving Environmental and Occupational Health Standards* 106–11 (Wiley1978) (declaring that the threshold dose-response model has "been the cornerstone on which industrial health standards have been derived in the United States for

II. REGULATORY AGENCIES FAIL TO VALIDATE THE THRESHOLD MODEL

The threshold model quickly became dominant in science and medicine. It became mainstream in all university textbooks, regulations for testing, data interpretation, and risk assessment.[8] There was a major factor that was overlooked, however. No person or group during the entire period of the twentieth century ever attempted to validate the capacity of the threshold dose-response to make accurate predictions in the below-threshold zone (that is, the zone where most people live for the vast majority of each day). The medical, scientific, and regulatory communities simply assumed that the threshold dose-response model would provide reliable predictions of responses to doses below the toxicological threshold.

For reasons that are not clear, these communities let this fundamental question of model validation go unanswered.[9] Several years ago our group at the University of Massachusetts Amherst sought to put the hormetic dose-response model through a validation test. Never having attempted this before, we explored how the scientific, medical, and regulatory communities may have vetted the threshold model. Perhaps we could learn from reviewing this experience. However, after many months of searching for an answer to this question of threshold dose-response model validation, we came to the tentative conclusion that, in fact, such validation had never been done. While we could never be certain since one cannot prove a negative, our continued searching has never yielded such a validation. In my opinion it most likely was never done—that is, until we finally put the threshold, hormesis, and Linear No-Threshold (LNT) models to the test (actually, three substantial validation tests). In each of these tests the threshold and LNT models made poor predictions of responses in the low-dose zone.[10] Only the hormetic (biphasic) dose-response made consistently accurate predictions. In addition, many thousands of other examples of

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some 30 years" and detailing EPA and other studies regarding a variety of environmental and health concerns).

8 See Calabrese, 30 Envir Toxicology & Chemistry at 2658–59 (cited in note 1).

9 It may be speculated that the failure to attempt to validate the threshold model simply resulted from failure of leadership on this issue, that no one considered the need to do it, or that, in fact, the leadership feared that the homeopathic (biphasic) model might prove to be superior.

10 See generally Edward J. Calabrese, et al, *Hormesis in High-Throughput Screening of Antibacterial Compounds in* E coli, 29 Hum & Experimental Toxicology 667 (2010) (studying the effect of antibacterial compounds on growth of *E coli* bacterium demonstrates that compounds stimulate growth at some concentrations below the threshold of toxicity); Edward J. Calabrese, et al, *Hormesis Predicts Low-Dose Responses Better Than Threshold Models*, 27 Intl J Toxicology 369 (2008) (studying the effect of various chemicals on the growth of yeast strains demonstrates that yeast exposed to nontoxic concentrations of chemicals grew more than the threshold model would predict); Edward J. Calabrese, et al, *Hormesis Outperforms Threshold Model in National Cancer Institute Antitumor Drug Screening Database*, 94 Toxicological Sci 368 (2006) (studying the effect of various chemicals on growth of yeast strains demonstrates that growth patterns of yeast exposed to nontoxic concentrations of chemicals are more often hormetic than they are consistent with the threshold model).

hormetic dose-responses have been published and summarized, further challenging the credibility of the threshold dose-response model.[11]

What should this mean for toxicology, risk assessment, and regulation? It strongly suggests that the toxicological community got the dose response at least half wrong—that is, it misunderstood the low-dose-response zone. Unfortunately, the entire "regulatory Bible" was based upon the threshold dose-response model including education, testing, regulation, and legislation. So now after sixty years we discover that not only has the US risk assessment practice been based on a nonvalidated and poorly performing model but so too has the entire world's!

The implications of the use of a poorly performing model are profound, as it affects the risk assessment process and ultimately how resources are allocated, the credibility of governmental agencies, and the public health. How did this happen? It occurred because of (1) a long-festering dispute between traditional medicine and homeopathy; (2) history's long reach, in which actions taken long ago for reasons that may not be appreciated today became entrenched and codified; (3) new issues that came to take precedence; and (4) past decisions made within an historical context that were assumed to be correct. EPA therefore ignored the dose-response history, accepting historical errors, and then became focused on specific questions and issues as required by the US Congress, such as how to regulate lead, mercury, PCBs, dioxin, and hundreds of other agents. Yet, it pursued these vital tasks while following a failed toxicological road map.

III. LNT—ACCEPTANCE AND MULLER'S DECEIT

While the scientific, medical, and regulatory communities got the dose response wrong with respect to the threshold model, they also made a serious error when they decided to abandon the threshold dose-response model for the LNT. The LNT model is applied to carcinogens (chemicals and ionizing radiation). This model assumes there is no safe level of exposure: exposure even to a single carcinogen molecule or ionization brings with it a risk of cancer. The change from threshold to linearity at low dose was an effort that was principally led by one person, the radiation geneticist, Dr. Hermann J. Muller. The push for a switch from threshold to LNT started soon after Muller made the discovery that X-rays could cause mutations in the germ cells of male fruit flies in 1927.[12] His one-man crusade drew others, especially those from his own community of radiation geneticists. Despite frustrations and setbacks, Muller's influence grew as his

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11 See, for example, Edward J. Calabrese and Robyn Blain, *The Occurrence of Hormetic Dose Responses in the Toxicological Literature, the Hormesis Database: An Overview*, 202 Toxicology & Applied Pharmacology 289, 291 (2005) (describing the authors' database of 1,450 articles containing findings of 5,600 hormetic dose-responses).

12 See H.J. Muller, *Artificial Transmutation of the Gene*, 66 Sci 84, 85–87 (1927).

work and its implications challenged those overseeing health issues, especially those concerned with occupational and patient exposures to X-rays and gamma rays. However, it took the dropping of the atomic bomb to propel Muller to the pinnacle of scientific recognition. In 1946 Muller was awarded the Nobel Prize for his 1927 discovery.[13]

During Muller's Nobel Prize Lecture of December 12, 1946, he adamantly stated that the threshold dose-response had to be replaced with the LNT model and that the threshold model no longer had any justification.[14] His lecture crystallized a major turning point against the threshold model, and it ushered in the publication of several key papers[15] from the University of Rochester that were funded by the Manhattan Project, for which Muller was a paid consultant.[16] During this time Muller and his radiation-geneticist colleagues continued to keep the pressure on various government regulatory agencies and advisory bodies. This mounting pressure came together in 1955 with the creation of the National Academy of Sciences (NAS) Biological Effects of Atomic Radiation ("BEAR I") Committee. Finally gaining a committee stacked in his favor, Muller drove this committee to replace the threshold model with the LNT.[17] Given the prestige

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13 See Edward J. Calabrese, *Muller's Nobel Lecture on Dose-Response for Ionizing Radiation: Ideology or Science?*, 85 Arch Toxicology 1495, 1495 (2011).

14 See Hermann J. Muller, *The Production of Mutations*, in 3 *Nobel Lectures in Molecular Biology, 1933–1975* 25, 25–42 (Elsevier 1977) (describing Muller's groundbreaking work on radiation and declaring that there is "no escape from the conclusion that there is no threshold dose" for ionizing radiation-induced germ cell mutation).

15 Ernst Caspari and Curt Stern, *The Influence of Chronic Irradiation with Gamma-Rays at Low Dosages on the Mutation Rate in* Drosophila Melanogaster, 33 Genetics 75 (1948) (describing the experiment and noting that results challenge the purportedly linear relationship between mutation and gamma radiation dose at low dose levels); Warren P. Spencer and Curt Stern, *Experiments to Test the Validity of the Linear R-Dose/Mutation Frequency Relation in Drosophila at Low Dosage*, 33 Genetics 43 (1948) (showing that linear relationship between X-ray dose and mutation in fruit flies holds at low dosages).

The papers were originally classified by the US government. During 1947 both papers were declassified and permitted to be published. Both papers were published in the journal *Genetics*. They were submitted for publication on November 25, 1947 and published in January 1948. Due to the very tight time schedule and the copious length of each manuscript, it is highly doubtful that they were peer-reviewed. Since the Editor-in-Chief was Curt Stern, a co-author on both manuscripts, it appears that he may have circumvented the normal peer-review process. See Edward J. Calabrese, *Key Studies Used to Support Cancer Risk Assessment Questioned*, 52 Envir & Molecular Mutagenesis 595 (2011) (discussing the history and declassification of the Caspari and Stern papers).

16 See generally Letter from Dr. Curt Stern to Dr. H.J. Muller (Sept 24, 1946) (on file with author); Letter from Dr. Curt Stern to Dr. H.J. Muller (Nov 5, 1946) (on file with author); Letter from Dr. H.J. Muller to Dr. Curt Stern (Nov 12, 1946) (on file with author); Letter from Dr. H.J. Muller to Dr. Curt Stern (Jan 14 1947) (on file with author).

17 National Academy of Sciences—National Research Council, *The Biological Effects of Atomic Radiation: Summary Reports from a Study by the National Academy of Sciences* 16 (1956) ("The probable number of additional induced mutations . . . is by and large proportional to the total dose of extra radiation. . . . To the best of our present knowledge, if we increase the radiation by X%, the gene mutations caused by radiation will also be increased by X%."); id at 3 ("There is no minimum amount of radiation which must be exceeded before mutations occur. . . . The more radiation, the more mutations.").

of the NAS, other national and international advisory groups quickly adopted the recommendations of the NAS and even expanded it from only addressing reproductive cells to that of somatic cells and thus cancer risks. Muller's efforts were so successful that they were eventually applied to the domain of chemical carcinogens by yet another NAS committee some twenty years later, citing the actions of Muller's committee.[18] Thus, the research and scientific leadership of Muller was strikingly influential, affecting carcinogen risk assessment policy in the United States and throughout the world.

A significant problem has recently arisen about the efforts of Muller during this 1946–56 period. Newly disclosed correspondence has now revealed that Muller was aware of the results of a major study by Ernst Caspari and Curt Stern from the University of Rochester on the effects of chronic exposure to ionizing radiation on the germ cells of fruit flies, finished in the fall of 1946.[19] The findings of this study, the most substantial one up to that point in the field, did not support a linear interpretation but rather a threshold model. In fact, Muller had become aware of this study about five weeks prior to the Nobel Prize Lecture when Stern sent him a copy of the data and supporting paper.[20] Within a week of the receipt of the data and paper, Muller acknowledged the challenge of these findings to the LNT model and the high quality of the work in a return letter to Stern.[21] A few weeks after the Nobel Prize lecture he again affirmed his support for the quality of the study, how it challenged the LNT concept, and the need to replicate the findings as soon as possible in a detailed letter to Stern.[22] Yet, Muller would tell the Nobel Prize Lecture audience that there was no scientific value or predictive utility with the threshold model—that is, this model must be dropped.[23]

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18 Safe Drinking Water Committee, *Drinking Water and Health* 47–49 (National Academy of Sciences 1977) (discussing the effect of carcinogens on humans at low doses and maintaining that the effect of low-level exposure is "well approximated by a simple linear function of dose").

19 See generally Edward J. Calabrese, *Muller's Nobel Prize Lecture: When Ideology Prevailed over Science*, 126 Toxicological Sci 1 (2012); Calabrese, 52 Envir & Molecular Mutagenesis 595 (cited in note 15) (identifying flaws in papers authored by Curt Stern that were used to support adoption of LNT, or linear, dose-response models in risk assessment); Edward J. Calabrese, *Muller's Nobel Lecture on Dose-Response for Ionizing Radiation: Ideology or Science?*, 85 Arch Toxicology 1495 (2011) (criticizing Muller and providing excerpts of letters between Muller and Stern indicating that Muller was aware that a study authored by Stern and Caspari called his linear dose-response theory for radiation-induced germ cell mutations into question).

20 See Calabrese, 126 Toxicological Sci at 1 (cited in note 19), citing Calabrese, 85 Arch Toxicology at 1496–97(cited in note 19).

21 See Calabrese, 85 Arch Toxicology at 1496 (cited in note 19) (excerpting letters between Muller and Stern before the Nobel Prize Lecture).

22 See id at 1497 (analyzing a January 14, 1947 letter from Muller to Stern).

23 Muller, *The Production of Mutations* at 30 (cited in note 14) ("There is no threshold dose, and [ ] individual mutations result from individual hits producing genetic effects in their immediate neighborhood.").

While the striking dishonesty of Muller was revealed in these letters, what followed next was an elaborate cover-up plan to both save Muller's reputation for lying during his Nobel Prize Lecture and promote the acceptance of the LNT.[24] This was led by Stern, along with the help of Muller and other lesser notables, as well as the journals *Genetics* (where Stern was the Editor-in-Chief) and *Science*.[25] The actions of Stern, Muller, and others have been carefully reconstructed and documented as a result of obtaining newly released correspondence and now-declassified documents.

CONCLUSION

The current US risk assessment policy for ionizing radiation and chemical carcinogens was born from the womb of blatant dishonesty within a framework of ideological science. These recent discoveries of the historical record are important as they not only force a rewriting of the history of environmental health and risk assessment but also call for a reassessment of risk assessment policies that are currently fully operational but that were based on both a lack of validation and deliberate deception. This is the risk assessment history of the United States and until society gets these issues correct, the issue of pollutant allocation proposed by Professor Arden Rowell may have to wait.[26]

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[24] See Calabrese, 52 Envir & Molecular Mutagenesis at 597–602 (cited in note 19) (analyzing circumstantial evidence showing the multiple steps Stern, Muller, and others took to marginalize support for the threshold model).

[25] See id at 599–602.

[26] See Arden Rowell, *Allocating Pollution*, 79 U Chi L Rev 985 (2012).