Calabrese says mistake led to adopting the LNT model in toxicology

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Edward Calabrese, the University of Massachusetts Amherst environmental toxicologist who has long been a critic of the current linear no-threshold (LNT) approach to risk assessment for radiation and toxic chemicals, argues in a new publication that the U.S. National Academy of Sciences (NAS) made an error in adopting the LNT because the research findings on which they relied contained a fundamental error, unknown to them and only discovered decades later.

Calabrese says, "My research reveals for the first time that had that error been corrected or never made in the first place, the evidence for radiation-induced mutation would have strongly supported a threshold rather than a linear dose response. This finding indicates that the LNT-based cancer risk assessment used by the U.S. government and other countries was based on a mistake." This challenges the accuracy, validity and cost-benefit analyses of exposure standards for carcinogens, he adds.

In a recent issue of *Environmental Research*, Calabrese asserts that had the error in the major findings of William Russell, a member of the NAS Genetics Panel, been corrected, "fundamental beliefs and assumptions" about the effects of ionizing radiation would have been challenged, yielding "profound implications" for risk assessment.

A professor in UMass Amherst's School of Public Health and Health Sciences, Calabrese says that Russell's 1958 paper in *Science* and subsequent research documented "evidence of a significant discovery that threatened the underlying tenets supporting the linear no-threshold

dose response model." He adds that Russell later acknowledged a significant under-reporting of the mutation rate of the historical control group that led to the mistaken adoption of the LNT by the EPA and other regulatory agencies and advisory bodies.

Further, Calabrese says, Russell's "sustained, respected, and painstaking work in observing and documenting the effects of radiation on mice indicated that the rate at which radiation dose was administered made a major difference in the measured mutation rate for the identical total dose." The corrected Russell research indicates that when the dose-rate of radiation is sufficiently reduced or lowered the radiation failed to induce mutations, achieving a safe level of exposure, he adds.

This evidence, the UMass Amherst researcher says, led the NAS committee to "incorrectly adopt the LNT model, which was a decision that profoundly changed the course of risk assessment for radiation and chemicals to the present."

Calabrese's paper recalls Russell's two decades of dose-rate research for ionizing radiation in well over 1 million mice, replacing fruit fly experiments with a model more relevant to humans. Russell concluded that six major hypotheses about ionizing radiation and gene mutation were not supported by data. Calabrese notes, "This should have been a major galvanizing event that led to substantial debate while offering an opportunity for a significant mid-course correction concerning the nature of the dose-response in the low DOSE/dose-rate zone, but it failed to do so."

Calabrese says Russell failed to expand upon and champion his own findings and to elaborate on their "broad health and societal implications." As the field of toxicology was transformed and researchers began to evaluate not only radiation but chemicals for mutagenicity and carcinogenicity, Russell's failure to "provide the

sufficient leadership" contributed to his experimental data being ignored in discussions of dose-response.

Russell's only radiation genetics graduate student later found that Russell had failed to report spontaneous mutations and had made other errors in several studies. Subsequent correction of the record after a Department of Energy investigation was not widely publicized and remained "guarded information," Calabrese notes. "It may seem strange that a mistake on such a critical question as estimation of mutation frequency was not detected and corrected early on," he writes. But at the time few research groups could handle the questions raised, he adds. Calabrese ends by summarizing factors that could have changed cancer risk assessment. He quotes James Crow, chair of the Biologic Effects of Ionizing Radiation I genetics subcommittee, who wrote that the "alarmist views" of the original committee and its intellectual leader, Hermann Muller, were "too effective in cautioning against radiation risks, with the result that the public now has an irrational fear of low-level radiation relative to other risks." Further, Calabrese reports that Crow wrote, "The fear, I suppose, has resulted more from the assumption of no threshold for carcinogenic effects than from the dread of genetic effects. In any event, the battle that Muller waged was certainly won: the present standards for radiation safety are more stringent than even he dared advocate."

Calabrese has for many years advocated for hormesis, a dose-response risk assessment model he says provides evidence that low-dose exposure of some chemicals and ionizing radiation is benign or even helpful. Last year, he and colleagues at George Mason University and in the Netherlands suggested that despite the fact that the LNT model was adopted in the 1950s as the gold standard "without adequate validation," they do not propose to replace the LNT with a hormesis dose-response model. Instead they wish to reconcile the two to offer "optimal public health protection."

More information: Edward J. Calabrese, The threshold vs LNT showdown: Dose rate findings exposed flaws in the LNT model part 1. The Russell-Muller debate, *Environmental Research* (2017). DOI: 10.1016/j.envres.2016.12.006

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