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Paper and Session Title: Where There's a Will, There's a Wave: No Safe Dose?

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Introduction

The linear no threshold model of carcinogenesis (LNT) assumes that all exposures to carcinogens, including asbestos, cause irreversible and, hence, cumulative damage to DNA down to the lowest possible doses in proportion to the amount of exposure. The model is the major basis for the claim that no dose of asbestos or any carcinogen is safe even at the lowest dose. Consistent with the model's expression of cumulative damage and with the claim of no safe dose, plaintiffs argue that every exposure to asbestos, whether occupational, take home, or environmental, contributes to cumulative exposure causing mesothelioma.

When these claims are presented as the view of a consensus of scientists or the uniform view of the regulatory agencies and other organizations, courts can be lulled into acceptance; however, the claims that there is no safe dose and that each exposure contributes to cause cancer are specious. The LNT model underlying these claims is bereft of scientific basis or validity.

The model is beset a sordid history of the model, including suppression of research results, creation of false "science" in support of the model, and a general lack of consideration of anything contrary to the model. Regulatory agencies adopted the model, not due to scientific study, but rather due to its ease of application and for the apparent lack of another alternative. More recently, organizations and scientists have presented critiques and refutations of the model,

belying the idea that it is the result of some sort of a consensus. Even the "low dose" epidemiological studies on asbestos that plaintiffs and their experts continually cite are largely inconsistent with the model. In the end, the modern understanding of DNA repair is wholly inconsistent with any conclusion that carcinogenic damage to DNA is irreversible and thereby refutes the validity of any conclusion that exposures to carcinogens and resulting damage to DNA are cumulative in the causation of the disease.

Defining LNT

Although not always defined in the same terms, the Linear No Threshold model of carcinogenesis always involves the following several concepts:

1. Carcinogens can and do cause damage to DNA.
2. The damage is irreparable and irreversible,
3. The damage is cumulative, i.e. higher or additional doses constantly add to the risk regardless of time frame.
4. The risk of cancer increases in a linear relationship to cumulative dose.
5. Risk increases at any exposure exceeding zero, i.e. there is no threshold or safe dose.

LNT assumes that the total dose causes cancer. The time over which the dose is experienced is, hence, assumed to be irrelevant.

A Short History of LNT and its Early Application to Radiation

The idea of something akin to LNT arose originally from thoughts that environmental radiation caused mutations explaining the changes in humans and other species under Darwin's Theory of Evolution. Ultimately, research would demonstrate that environmental radiation was only $1/1300^{th}$ of the level needed to cause the type and level of mutation consistent with Darwinian Evolution. Calabrese, E.J. "The linear No Threshold dose response model: A comprehensive assessment of its historical and scientific foundations." Chemico-Biological Interactions. Vol. 301 (2019) at 6-8. The explanation of the mechanism of evolution would wait some number of decades. In the meantime, the concept would find another use.

In 1927, based on experiments subjecting male fruit flies to high dose X-rays, Hermann J. Muller found phenotypic changes in subsequent generations and published his finding as proof of "artificial transmutation of the gene," in other words, gene mutations. Muller, H.J. "Artificial Transmutation of the Gene." Science Vol. 66, Number 1699 (1927) at 84. Although Muller's studies used very high doses of radiation, he assumed that the dose response was linear down to a single radiation event at the lowest dose. There was dissent. Lewis J. Stadler's work at the University of Missouri involved 13 doses of radiation to barley with the lowest doses "showing no enhanced mutation over the control." He argued that Muller had only induced large chromosomal deletions, not point gene mutations. Calabrese, Comprehensive Assessment, supra. at 6-12.

In 1946, based upon radiation experiments that were part of the Manhattan Project, Ernest Caspari reported to his superior, Curt Stern, that the total dose did not cause genetic change and that there was in fact a threshold or "tolerance" dose. Muller, when he accepted his Nobel Prize in 1946 and gave his acceptance speech lauding LNT, at the time calling it the proportionality rule. Unbelievably at that very time Muller had the Caspari data in his possession. The Caspari data never had much impact. Caspari's superior, Stern, along with a co-author, published support for the LNT model in Science. While mentioning Caspari's work, the underlying data from Caspari was not included, giving a false impression of support for the model. Id.

In the 1950s, Warren Weaver chaired the Biological Effects of Atomic Radiation (BEAR I) Genetics Panel. Prior to this Panel, medical professionals accepted a threshold model. Government agencies utilized a threshold model. Muller's colleague, Tracy Sonneborn, defined LNT for the Panel explaining that all mutational radiation damage was "cumulative, irreversible, and lacking repair" with dose related to damage in a "linear" manner "down to a single ionization." To prove the value of LNT, Weaver asked the twelve members of the Panel to estimate genetic damage over ten generations from a radiation event to the American public. Three Panelists refused to participate; the estimates would simply be too uncertain. James Crow reviewed the submitted estimates and told Weaver that there was so much variation in the estimates that LNT would have little credibility if the estimates were published. To save LNT, the BEAR Genetics Panel published the estimates, but only after eliminating the three lowest estimates and without disclosure of the refusal of some Panel members to participate. Elimination of these estimates brought the statistical uncertainty from 4000-fold to 750-fold. The estimates that were ultimately published were by fiat dropped to a 100-fold level of uncertainty. Calabrese, Comprehensive Assessment, supra. at 6-12.

James Neel of the University of Michigan was one of the geneticists refusing to participate. The effects of the atomic bomb on Japanese population created an opportunity to study the generational effects of radiation, not on animals, but humans. The sample size was substantial, approximately 70,000 children born over a decade. Neel and others did the study under the auspices of the Atomic Bomb Casualty Commission of the National Academy of Science. The study revealed no statistically significant results from this radiation event. When speaking in panels and at conferences and when writing in letters to colleagues, Muller successfully blunted the bomb research results, arguing that the human data was too uncertain and that the fruit fly work was more reliable. His Nobel Prize as well as his commanding personality gave him the power to redirect the discussion in favor of LNT and away from the findings of Neel, a younger and less well-known researcher. Calabrese, Comprehensive Assessment, supra. at 12-15.

What came next should have put an end to LNT. First, it was discovered that the work of a Muller colleague, upon which Muller placed so much reliance, had been done with mature spermatozoa which had no ability to repair DNA damage. A threshold exists because DNA damage can be repaired. By using cells without the ability to repair DNA damage, the study provided no evidence to deny the existence of a threshold or to support a linear relationship

between dose and genetic damage causing cancer. Second, approximately 25 years after William Russell had done his original mouse study, Paul Selby, a student of Russell at the Oakridge National Laboratory, discovered a misconstruction in the mouse control group. Correcting the misconstruction meant that the incidence of mutation throughout the study group was so low that is demonstrated a clear threshold. Calabrese, Comprehensive Assessment, supra. at 15-19. Third, from 1956 through 1959, Russell conducted another experiment on the effects of radiation on adult mice showing clear evidence of a threshold. To avoid a conflict with LNT that would have adversely affected his research funding, Russell, motivated by ideology and self-interest, suppressed the results which were not published until 1993. Publication in the late 1950s or early 1960s at a key moment in the ongoing debate about LNT could have changed the course of that debate. Calabrese, E. et al. Cover up and Cancer Risk Assessment: Prominent US scientists suppressed evidence to promote adoption of LNT. Environmental Research. Vol. 210 (2022) at 112973.

Unfortunately, prior to the reconstruction of the Russell mouse data, the Biologic Effects of Ionizing Radiation (BEIR I) Genetics Sub-committee recommended LNT. BEIR I jumped to a conclusion supporting LNT before the full meaning of Russell's data was understood. Calabrese, Comprehensive Assessment, supra. at 15-19. Calabrese gives this conclusion about LNT:

> "The LNT single-hit dose-response model for cancer risk assessment was conceived, formulated, and applied in a manner which is now known to have been scientifically invalid. . . [T]he concept of LNT . . . is shown to have multiple flaws that reveal its lack of scientific validity. . . [T]he basis for cancer risk assessment as recommended by NAS BEIR I Subcommittee and accepted by virtually all regulatory agencies, is demonstrably incorrect."

Calabrese, Comprehensive Assessment, supra. at 21. To play upon and inflame fears in a jury, plaintiffs' attorneys claim that there is "no safe dose," citing regulatory pronouncements based upon the scientifically invalid LNT model.

OSHA and the EPA

In the 1970s, charged with risk assessment for carcinogens, OSHA and EPA searched for a principle or model of carcinogenesis arising from exposures to chemicals and minerals. Although previously applied only to radiation, the agencies turned to LNT.

In 1978 OSHA held hearings with some scientists advocating in favor of the linear model. Some industry witnesses criticized the LNT concept, but the most authoritative critics of LNT at the time were Hermann Druckrey and Alexander Grendon. For reasons unknown, neither testified at the OSHA hearings. With a clearly one-sided presentation on the subject, OSHA could easily dismiss any criticism of the LNT model. Calabrese, E. J. et al. "Thresholds for Carcinogens." Chemico-Biological Interactions. 341 (2021) at 109464.

Toxicologist Roy Albert led a similar effort at the EPA in the mid to late 1970s. One of the people taking the lead at the EPA was toxicologist Roy Albert. The EPA did not hold hearings, but, rather, evaluated the matter internally through one or more committees. Albert defined the "linear non threshold dose-response model . . . [as] the single most powerful idea in carcinogen risk assessment. It means that only zero dose produces zero risk. Any dose, however small, has an estimable risk." Albert, R.E. "Carcinogen Risk Assessment in the U.S. Environmental Protection Agency." Critical Reviews in Toxicology. Vol. 24(1) (1994) at 75, 80. The EPA based such conclusion on the assumption that the effects of carcinogens were "to a large extent irreversible." Asbestos Information Association, Second Annual Conference (September 10-11, 1975).

Was it scientific data or something else that led to such conclusions or, more appropriately, assumptions? The EPA in fact merely tended to follow the precedent of other agencies, most importantly, the Atomic Energy Commission (AEC) that applied LNT to radiation exposure and literally "waved aside" any difference between radiation and chemical carcinogens. With honest hindsight, in 1994, Albert provided the most basic reason for the EPA's adoption of LNT—it was "Extremely simple to use." Albert, supra.

Neither the EPA nor OSHA engaged in any scientific effort to demonstrate that LNT was somehow applicable to carcinogens other than radiation, particularly considering that the application of LNT to radiation was erroneous in the first place.

Cumulative and Irreversible?

The human body has defense mechanisms to the occurrence of carcinogenesis, including DNA repair, enzymatic detoxification, cell cycle control, apoptosis, necrosis, and the immune system. See Fukushima, S. et al in Thresholds for Carcinogens: From Mechanisms to Regulation. Nohmi, T. and Fukushima, S. ed. (Academic Press, Amsterdam: 2021) at 13. The most interesting and consequential regarding LNT is DNA repair. LNT assumes that all genetic damage due to carcinogens is cumulative in the causation of cancer. As a result, for all damage to be cumulative, the proponents of LNT must also posit that each and every event damaging to DNA is irreversible. If an exposure to a carcinogen causes no damage to DNA it cannot be cumulative. If damage to DNA from an exposure to a carcinogen is subject to repair, it cannot be irreversible and, again, not cumulative.

If OSHA and the EPA had closely followed scientific developments, particularly relating to DNA repair, those regulatory agencies may not have so quickly adopted LNT. In the early 1970s a discovery by Tomas Lindahl changed the entire scientific conversation about DNA. Previously, DNA was thought to be stable, unchanging, almost immutable unless subjected to insult by some DNA damaging event. Lindahl showed the "limited chemical stability" of DNA even without the influence of environmental attack. DNA, according to Lindahl's research, was constantly subjected to chemical reactions threatening its integrity. Lindahl called this "DNA

decay." If DNA was unstable, Lindahl thought that there must be a mechanism to keep or repair the integrity of the DNA. In answer to his own question, in 1974 and 1976, he published his identification of the first two DNA repair proteins and proposed the model of DNA repair known as base excision repair. Gustafsson, C. Scientific Background on the Nobel Prize: Mechanistic Studies of DNA Repair. (Kungl Vetenskaps-Akademien, 2015) at 6-7.

Today, DNA repair is a well-known phenomenon. In fact, the beneficial effects of DNA repair are now so widely appreciated and accepted that the Nobel Prize committee gave its award in chemistry in 2015 to Aziz Sancar, Tomas Lindahl, and Paul Modrich for their discovery of mechanisms of DNA repair. As humans, indeed, all livings organisms, are exposed to many sorts of environmental insults damaging to DNA, "robust" repair mechanisms "faithfully" protect DNA. Kanakoglou, supra. Chatterjee, N. and Walker, G. "Mechanisms of DNA Damage, Repair and Mutagenesis." Environmental and Molecular Mutagenesis. Vol. 58(5) (2017) at 1, 4. The functions of DNA repair led Golden, Calabrese, and Bus to opine that "the ever-growing mountain of evidence directly challeng[es] the biological underpinnings of the LNT model." Golden, R. et al. "An Examination of the Linear No-Threshold Hypothesis of Cancer Risk Assessment: Introduction to a Series of Review Documenting the Lack of Biological Plausibility of LNT." Chemico-Biological Interactions. Vol. 301 (2019) at 4.

The potentially damaging effects of asbestos are subject to counteraction by the mechanisms of DNA repair. A sufficient dose of asbestos, depending on type and fiber dimension, will cause oxidant creation (reactive oxygen species, "ROS") and chronic inflammation. If sustained long enough and severely enough, the inflammation will cause damage to DNA that is irreparable. Mossman, B.T. et al. "New Insights into Understanding the Mechanisms, Pathogenesis, and Management of Malignant Mesotheliomas." The American Journal of Pathology. Vol. 182, No. 4 (2013) at 1065, 1070; Cox, L.A. "Dose-response modeling of NLRP3 inflammasome-mediated diseases: asbestos, lung cancer, and malignant mesothelioma as examples." Critical Reviews in Toxicology. Vol. 49(7) (2019) at 614-635.

As part of the process of inflammation, the effects of radiation or various chemicals increase the production of ROS which in turn attack DNA introducing various changes in the bases of the DNA. Repair mechanisms remove or correct the damaged bases. See Nohmi, T. et al in Thresholds for Carcinogens: From Mechanisms to Regulation. Nohmi, T. and Fukushima, S. ed. (Academic Press, Amsterdam: 2021) at 55. "[M]ore than 100 oxidative lesions damaging to DNA have been discovered. Most of these are corrected by base excision repair." Gustafsson, supra. at 8.

LNT: Not A Consensus View

Although consensus is not an appropriate method to evaluate the validity of a scientific hypothesis, any claim that LNT is a consensus view is not correct. Edward Calabrese, so often cited in this article, is not alone in his criticism of LNT. Bruce Ames is likely the scientist most

deserving of the Nobel Prize who has never won it. His Ames test is an expeditious and inexpensive method to determine mutagenicity and thereby carcinogenicity of substances. Despite his attention to issues of cancer, he is extraordinarily cautious about overstatement of the dangers of carcinogens: "cancer estimates for toxin control programs are worst-case, hypothetical estimates, and the true risks at low dose are often likely to be zero." Ames, B. et al. "Environmental Pollution, Pesticides, and the Prevention of Cancer: Misconceptions." The FASEB Journal. Vol 11 (November 1997) at 1042, 1050.

Neither the 11,000 member American Nuclear Society nor the 6000 member Health Physics Society accept the LNT model for radiation, the carcinogen for which the model was originally conceived. Professor Wade Allison of Oxford University and Professor Bernard Cohen of the University of Pittsburgh refuse to support the LNT concept. Even Dr. Michael Repacholi of the WHO admits that LNT is an assumption from observation about the effects of high levels of radiation. See:

> https://www2.nau.edu/lrm22/lessons/scientific_method/scientific_method.html
> https://www.colby.edu/biology/BI17x/expt_method.html
> https://www.ft.com/content/c49c8472-767b-11dc-ad83-0000779fd2ac
> https://www.chemeurope.com/en/encyclopedia/Linear_no-threshold_model.html

One issue of the prestigious journal Chemico-Biological Interactions contained articles by scientist after scientist refusing to support and in fact refuting the basis for the LNT model of carcinogenesis. They included R. Golden, J. Bus, E. Calabrese, David Costantini, Benny Borremans, Bobby R. Scott, Sujeenthar Tharmalingam, Shayenthiran Sreetharan, and Antone L. Brooks. Chemico-Biological Interactions. Vol. 301 (2019) at 2-67.

Government agencies are not uniformly in support the LNT model as a predictor of cancer risk from asbestos. Food and Drug Administration, Department of Health and Human Services, letter from Linda L. Taylor, Ph.D. to Debbie Krathen, dated April 17, 1981 ("asbestos is known to be a carcinogen when inhaled in large quantities"). In 2017, the National Institute for Occupational Safety and Health (NIOSH) caught up with science. At least for carcinogens, like asbestos, that act through a non-genotoxic mechanism such as inflammation, NIOSH recognized that at low doses the risk may be "non-linear" and include a "threshold below which there is no added risk." Department of Health and Human Services, Centers for Disease Control and Prevention, National institute for Occupational Safety and Health. NIOSH Chemical Carcinogen Policy: Current Intelligence Bulletin 68. (July 2017) at 19.

Epidemiology and LNT

Plaintiffs and their experts often cite several epidemiological studies of asbestos and mesothelioma in support of causation, particularly involving low dose exposures. Offermans, N.S.M. et al "Occupational Asbestos Exposure and Risk of Pleural Mesothelioma, Ling Cancer,

and Laryngeal Cancer in Prospective Netherlands Cohort Study" Journal of Occupational and Environmental Medicine. Vol. 56 (2014) at 6; Rodelsperger, K. et al. "Asbestos and Man Made Viteous Fibers as Risk Factors for Diffuse Malignant Mesothelioma: Results from a German Hospital-Based Case-Control Study." American Journal of Industrial Medicine Vol. 39 (2001) at 262; Iwatsubo, Y. et al. "Pleural Mesothelioma: Dose-Response Relation at Low Levels of Asbestos Exposure in a French Population-based Case-Control Study." American Journal of Epidemiology. Vol. 148(2) (1998) at 133; Lacourt, A. et al. "Attributable Risk in Men in Two French Case-Control Studies on Mesothelioma and Asbestos." European Journal of Epidemiology. (September 7, 2010); Lacourt, A. et al. "Co-exposure to refractory ceramic fibres and asbestos and risk of mesothelioma." Cancer and Occupational Lung Disease. Vol. 44 (2014) at 725; Lacourt, A. et al "Occupational and Non-occupational Attributable Risk of Asbestos Exposure for Malignant Pleural Mesothelioma." Thorax Online. doi:10.1136/thoraxjnl-2013-203744 (2/11/2014) at 1, 5 (99% confidence interval); Jiang, Z. et al. "Hand-spinning Chrysotile Exposure and the Risk of Malignant Mesothelioma: A Case-control Study of Southeastern China." International Journal of Cancer. Vol. 142 (2018) at 514.

These studies lack reliability due to bias inherent in their methodology, fail in most instances to define the fiber types allegedly causing disease, and do not disclose the identity of industrial hygienists estimating exposures. Siemiatycki, J. et al. "Invited Commentary: Is It Possible to Investigate the Quantitative Relation between Asbestos and Mesothelioma in a Community-based Study?" American Journal of Epidemiology. Vol. 148(2) (1998)(, "the dose-response relation derived in a given study would be strictly generalizable only to another population that experienced a mix of fiber types similar to the source population"); Zellmer, M. "Are Low Dose Asbestos Exposure Studies Unreliable?" Asbestos Columns (March, 2011) at 4; Zellmer, M. "Any Exposure Above Background: Is It Really Causative?" Asbestos Columns (February, 2015) at 4.

In any event, the risks determined by these studies are wholly inconsistent with the risks determined by LNT. For example, in the Offermans study risk is calculated as 2.69 greater than background from exposures of 0.2 f/cc-yrs while exposures of 1.58 f/cc-yrs yield an increased risk of 3.04. This is not what LNT would predict. Under LNT an exposure that is 7.9 times greater (1.58/0.2=7.9) should create a risk also 7.9 times greater; hence, increasing dose from 0.2 to 1.58 f/cc-yrs, LNT estimates that the risk should be 21.25, not 3.04.

LNT predicts risk of disease at any exposure, no matter how low, but these low dose epidemiological studies fail to confirm consistently that risk of disease occurs at all levels even at the lowest doses. Among the studies cited, these four studies show no statistically significant increased risk at the lowest doses of asbestos exposure:

Author/study	OR or RR for Lowest Dose Range
Offermans DOMJEM	4 yrs of exposure
Iwatsubo	0.0001-0.49 f/cc-yrs
Lacourt Study A	>0-1 f/cc-yrs
Lacourt 2014	>0-1 f/cc-yrs

Once again, these results demonstrate no consistency between the studies and LNT.

Interestingly, OSHA and the EPA which rely upon LNT to determine risk of disease from exposure fail to cite any of these epidemiological studies in support of their findings or regulations. Although admittedly somewhat speculative, it is likely that these agencies realize that the results of these epidemiological studies are not consistent with the results from LNT.

Conclusions

These inescapable conclusions may be drawn:

1. LNT lacks scientific validity as originally applied to radiation.
2. Regulatory agencies applied LNT to carcinogens other than radiation without appropriate work to verify such applicability.
3. Modern understanding of DNA repair, as well as other defense mechanisms of the human body, are wholly inconsistent with the concepts of LNT that any dose has risk and that all exposures are cumulative due to irreversible damage.
4. Even epidemiology often cited by plaintiffs is inconsistent with these same concepts of LNT, namely, that all doses, no matter how small, have risk and that genetic damage from exposure is cumulative because such damage is irreversible.
5. Because LNT lacks validity, any claim of “no safe dose” lacks validity.