No Validity to No Safe Dose: Part I - The Flawed Linear No Threshold Model of Carcinogenesis
A Commentary from Mark G. Zellmer of Husch Blackwell LLP

How Covid-19 Changed the Longest-Running Mass Tort in U.S. History: Asbestos Litigation
A Commentary from Treven Pyles, Administrative Director, Environmental Litigation Group, P.C.

Wash. Jury Reaches Defense Verdict For Boiler Refractory Manufacturer
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Author bio on page 9

The Linear No Threshold model of carcinogenesis ("LNT") holds that all exposures to carcinogens cumulatively increase the risk of cancer in a linear, proportional relationship to dose, even at the lowest possible levels of exposure. The LNT model, first postulated in the 1920s, is not the product of well-founded science and is subject to clear refutation by concepts of science today. In fact, the genesis, and then acceptance, of LNT is the result of decades of bluster, literal bullying (both verbal and financial in the scientific community), non-disclosure, and even deception.

The importance of LNT in asbestos, as well as other toxic tort, litigation is obvious. Plaintiffs' attorneys and their experts have a mantra recited repeatedly in depositions, reports, affidavits, and trials regarding asbestos or, for that matter, any toxic tort: "there is no safe dose of a carcinogen." In somewhat more lengthy terms, they explain that there is "no threshold below which an exposure to a carcinogen will not cause cancer." In the 216 pages of one of Dr. Arthur Frank's affidavits, he mentions "no safe dose" of asbestos 37 times. This does not even count the number of times that he opines that there is no "threshold" for exposure to asbestos. In the standard 46-page report of Dr. Edwin Holstein, he mentions "no safe dose" of asbestos 11 times.

Various organizations and agencies use LNT to justify findings on carcinogens and thereby give support, whether consciously or otherwise, to the claims of plaintiffs' attorneys. For example, since 1975, the Occupational Safety and Health Administration (OSHA) has "assumed" that there is "no safe threshold" for exposure to any carcinogen. In its response to public comments advocating that there is a threshold for causation of mesothelioma by chrysotile asbestos, the EPA rejected any such notion citing "accepted models for cancer" as well as the "linear" dose response model. The World Health Organization (WHO) rejects any concept of a "threshold" for the carcinogenic risk of asbestos.

The LNT model is used to support such statements and views expressed by plaintiffs' attorneys and their experts, as well as various agencies and organizations. Even when not mentioned expressly, LNT is the basis for what plaintiffs' attorneys argue in asbestos cases. Indeed, much of what plaintiffs' attorneys say in asbestos litigation would fail without the LNT concept.

This article will discuss the concepts underlying LNT and why the science supports a view clearly contrary to LNT:

• How LNT is defined?
• What is the history of LNT?
• How LNT is now applied to all carcinogens?
• What is the evidence of thresholds or safe doses?
• Why LNT is still utilized?

The conclusion is simply that LNT has no basis in science.

Defining LNT

Although not always defined in the same terms, the Linear No Threshold model of carcinogenesis always involves the following 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.
Testing these concepts is not straightforward. Errors in testing or in the interpretation of results can lead to erroneous findings. And, indeed, as research relating to LNT has progressed over the years, errors happened for any number of reasons. Anyone looking at this issue must understand some sense of the complexity of testing the concept of a linear no threshold model. For example, the study of carcinogenic exposure of cells that cannot repair DNA will not give worthwhile information on the cumulative nature of gene mutation. In a case-control animal study, if the control group of animals is not well controlled, the results may show risks where none actually exist.

Such testing involves test tubes and petri dishes or long observation of large numbers of animals. On the other hand, researchers have long recognized that the most relevant information on carcinogenesis in man comes from man himself. Determination of the risk of disease from past exposure can require estimates of exposure that is uncertain at best. Non-fatal occurrence of damage to DNA has been hypothesized to affect offspring for generations, but accounting for such occurrences among offspring requires careful, long-term observation.

Maybe most importantly of all, LNT assumes that the total dose is key to the occurrence of cancer. Failing to consider the time over which a dose of carcinogen is experienced (rate of administration of the doses) can leave this emphasis on total dose essentially unchallenged.

The Historical Perspective on LNT

Much, if not all, of what follows in this section comes from what Edward J. Calabrese has found regarding the development and acceptance of the Linear No Threshold model of carcinogenesis. The credit for uncovering so many of the elements of this story goes to him. His work and writing are equal parts history and science. The story is illuminating and fascinating. At its heart, it tells what can go wrong with science. Anyone wanting a more in-depth explanation can look to one or more of his many excellent articles. If you prefer to learn by listening, he has an online lecture on the subject that runs for almost an hour.

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. 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. Based upon further work of Muller’s under-study, Ray-Chaudhuri, Muller proposed that the damage from radiation was cumulative, meaning that the total dose created the gene mutation. 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. 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. Despite having the Caspari data in his possession, Muller lauded LNT in his 1946 Nobel Prize acceptance speech. 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.

In the early 1950s, Detlev Bonk, President of the Rockefeller Institute and the National Academy of Science, appointed Warren Weaver to chair 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. As part of an effort to negotiate the adoption of LNT,
Its importance in the context of this article is not the effect of hormesis from asbestos but rather the lack of any validity of the LNT model if hormesis is correct. The inconsistency is obvious. If low level exposures are beneficial in the prevention of mutation and cancer, low level exposures cannot create the risk of cancer.*

Weaver made his position clear at the start of the proceedings of the BEAR I Genetics Panel. Those who wanted funding should align their views to the accepted model, namely LNT. Thereafter, 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.” Not unexpectedly, the Panel adopted LNT. To prove LNT, Weaver asked the 12 members of the Panel to estimate genetic damage over 10 generations from a radiation event to the American public. Three Panelist refused to participate because any such estimates would be too uncertain to be reliable.

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 level of uncertainty of the calculations from 4000-fold to 750-fold. The estimates that were ultimately published were by fiat dropped to a 100-fold level of uncertainty.*

James Neel of the University of Michigan was one of the geneticists who refused to participate. Muller had found generational gene mutation from irradiation of fruit flies. The use of the atomic bomb at the end of World War II created the 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. Ultimately, the study extended over six decades. 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 the radiation event (i.e., dropping the atomic bomb) even though the radiation experienced was much higher than necessary to cause DNA damage in stem cells. 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.*

In the late 1950s, William Russell and co-authors at the Oakridge National Laboratory published the results of ionizing radiation to spermatogonia (undifferentiated male germ cells) and oocytes (loosely, female cells in the ovary) in a mouse model. The data for the oocytes, when analyzed by comparison to the control animals, showed that gene mutation was dependent upon dose rate. This meant that DNA damage was not cumulative, was reversible, and could not be assumed to be in linear relation to dose alone. There was a threshold.16 The data on the spermatogonia was less clear. Russell soft pedaled his data, saying that it needed to be interpreted carefully as a threshold may not be “a necessary consequence.”17 Once again, Muller fought to protect the LNT model, both in writing and presentations. Russell, the much younger scientist, like Neel before him, mainly deferred to Muller, the more senior, Nobel Prize winning researcher.*

What came next should have put an end to LNT. First, it was discovered that the work of Ray-Chaudhuri, upon which Muller placed so much reliance, had been done with mature spermatozoa which had no ability to repair DNA damage.*1 Muller and Ray-Chaudhuri, by using cells without the ability to repair DNA damage, did not have evidence to deny the existence of a threshold or to support a linear relationship between dose and genetic damage causing cancer. Second, after 25 years had elapsed from the revelations of Russell’s mouse data, Paul Selby, a student of Russell, also at Oakridge, discovered a misconstruction in the mouse control group. Correcting the misconstruc-
tion meant that the male mutation incidence was just as low as the female incidence. Hence, there was a threshold, consistent for both male and female mouse mutations. Unfortunately, prior to the reconstruction of the Russell mouse data, the Biologic Effects of Ionizing Radiation (BEIR I) Genetics Subcommittee recommended LNT. BEIR I jumped to a conclusion supporting LNT before the full meaning of Russell’s data was understood. Without reopening the matter for further scientific evaluation and discussion, the EPA and other agencies have adopted LNT.

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... The concept of LNT... is shown to have multiple flaws that reveal its lack of scientific validity... The basis for cancer risk assessment as recommended by NAS BEIR I Subcommittee and accepted by virtually all regulatory agencies, is demonstrably incorrect.”

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.

Application to All Carcinogens

The historical perspective emphasizes radiation and rightly so. Radiation was the focus of much of the 1940s, 1950s, and 1960s due to the bomb and nuclear energy. Agencies such as the EPA, like plaintiffs’ attorneys, do not limit the use of LNT to radiation alone, but, rather, apply it to all carcinogens. In 1994, Roy E. Albert, who at one time worked for the EPA on cancer risk assessment, asserted that genetic mutation, the cause of cancer, is “linear with radiation dose” and then further stated that the “difference between chemical carcinogens and ionizing radiation could be waved aside as they both cause genetic damage.” In the EPA’s recent response to public comments on its 2020 proposed findings on asbestos, it dismissed pages and pages of critical comments by a simple and short reference to its acceptance of the linear no threshold model of carcinogenesis. All of this creates a problem. LNT was originally developed as a radiation model. If the basis for LNT is not scientifically valid for radiation, it should not be valid for other carcinogens.

Thresholds, NOAELs, and More

The work of Stadler, Caspari, Neel, Russell, and now Calabrese as well as many others ultimately led to the dual conclusions that cells repair damage to DNA done by carcinogens and that the capability to repair damage to DNA leaves no doubt about the existence of a threshold dose. What is known about such thresholds for carcinogens, particularly asbestos?

Epidemiology

As mentioned earlier, the most relevant information on carcinogenesis in man comes from man himself. On that subject, the epidemiology of chrysotile asbestos is most illuminating.

Study of the chrysotile miners at Balangero found that the relative risk of mesothelioma from chrysotile exposure was statistically significant only when exposures reached 346 fibers-years. Epidemiology on the North Carolina textile cohort found that the statistically significant relative risk of mesothelioma from chrysotile exposure was 1.15 for 100 fibers-years of cumulative exposure. This result came from the inclusion of four pleural cancers with four cases of mesothelioma. The pleural cancers could be mesothelioma, but they could also be pseudo-mesotheliomatous lung cancer or metastasis from renal cancer or something else entirely. When only the four cases of mesothelioma were included, the relative risk of developing mesothelioma was not statistically significant.

An analysis of cohorts with chrysotile exposure led Pierce and co-authors to conclude in 2016 that the risk of mesothelioma will not increase from chrysotile exposure when the cumulative dose is less than approximately 200 fibers-years. The work of Pierce has been criticized because their identification of a “No-Observed-Adverse-Effects-Level” or NOAEL is confusing animal toxicology with human epidemiology. Such criticism is not fair. Even the EPA in its IRIS database uses the term “NOAEL” without distinction between animals and humans.

Likely, the most persuasive data comes from the Canadian chrysotile mining cohort. Even with known contamination of the ore with tremolite, no case of mesothelioma was identified in some 4000 men employed less than two years.

Lung Fiber Burden

When parenchymal lung tissue is removed and weighed, the tissue may be dissolved leaving the asbestos fibers to be counted. In 1960, Christopher Wagner first published on the relationship of mesothelioma and asbestos when he found numerous cases of mesothelioma in the crocidolite mining district of South Africa. On the other hand, he firmly believed that chrysotile was largely not responsible for the causation of mesothelioma. Gathering the evidence from lung digestion studies, human epidemiology, animal studies, and other sources, he estimated that mesothelioma would “occur when the fiber concentration is more than 1 million/g dry weight of [amphibole] fibers longer that 5.0
In 2019, Louis Anthony Cox returned to the issue of the number of fibers necessary to cause mesothelioma. He noted at the outset that the LNT model posited that a “single fiber” increased the risk of lung cancer and mesothelioma. His approach to test the LNT model varied from anything that had come before. He recognized that inflammatory response, and specifically chronic inflammation, induced by asbestos fibers was the key mediator in the development of one or more mutations and then cancer. The chronic inflammation was the result of the long-recognized problem of “frustrated phagocytosis” in which macrophages cannot engulf and destroy the long, biopersistent fibers. He then determined, by a mathematical model, that the threshold level for chronic inflammation in the target organ was at least hundreds of thousands to millions of these long, bio-persistent fibers per gram of dry weight lung tissue. The conclusions of Wagner and Cox are consistent.

**Animal Studies**

In 2014, Johnson et al. tested the linear no threshold hypothesis. Noting that others have challenged the no “safe level” or “no-threshold” assumption, the researchers administered F344 rats with aflatoxin B1 (AFB1), a potent hepatic toxin and carcinogen. They treated one group of rats with CDDO-Im, a drug known for its chemoprotective efficacy against hepatocellular carcinoma induced by AFB1. Of the rats with no CDDO-Im treatment, 96 percent developed liver cancer. Of the rats treated with CDDO-Im, none contracted liver cancer. If the LNT model was correct about the effect of low dose exposure to carcinogens with no threshold at all, at least some of the rats with CDDO-Im treatment should have suffered liver cancer. The authors concluded that “the absence of cancer... supports the concept of a threshold for obvious. If low level exposures are beneficial in the prevention of mutation and cancer, low level exposures cannot create the risk of cancer.

There is plenty of evidence of hormesis. Studies have shown a lack of any differences of DNA damage, cancer markers, or chromosomal aberrations between people living in areas of high background radiation versus those living in areas of low background radiation. In fact, organisms, including fruit flies (remember Hermann Muller) suffer negative effects on “fitness-related traits” from “lower-than background radiation levels.” In effect, stressing the system earlier in life can prepare the organism for stress later in life.

**Hormesis**

Hormesis is the beneficial “biologic process in which low doses of toxins elicit a protective response [against] a higher dose of the same toxins.” Hormesis is protective against various maladies including cancer. Its importance in the context of this article is not the effect of hormesis from asbestos but rather the lack of any validity of the LNT model if hormesis is correct. The inconsistency is

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**A Lesson From Bruce Ames**

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.”

**So, Why LNT?**

If the LNT model is so bereft of validity, why has it not been supplanted already?

First, the reason that it was adopted in a regulatory context still holds sway at this time. It is “extremely simple” to apply. That was the honest explanation given by Roy Albert from his involvement in the early days of the EPA’s early risk assessment. There is certainly not much scientific validity attended to a model used because it is simple.

Second, the adage of “follow the money” is applicable here. Regulators justify their work, and even their existence by scaring the public with overblown pronouncements of the risks of cancer. Plaintiffs’ attorneys make a fine living telling juries just how afraid that they must be of carcinogens. Government money seldom flows to those scientists who advocate lesser risk from carcinogens. There is an unconscious network of those that close ranks and criticize any challenge to LNT.
Third, there is inertia. It is hard to give up on a model having promoted it for decades, even though it is wrong. This is a certain intellectual stubbornness that is natural among us humans but needs to be resisted in the interests of science.

Conclusion

This article is only Part I. In the next article, Part II, which will run in the April 2021 issue of COLUMNS-Asbestos, the LNT model will be compared to epidemiology that plaintiffs so often present and rely upon. However, that epidemiology does not support and is inconsistent with the LNT model.

A conclusion can be drawn at this point: to win on a causation defense in toxic tort cases, and specifically in asbestos cases, defense attorneys must be prepared to challenge plaintiffs' constant refrain of "no safe dose" with a refrain of their own. Thresholds are real. LNT is not valid. It is plaintiffs selling a fiction.

Endnotes

1 The term “model” is used intentionally rather the term “theory.” In science a theory is a coherent proposition or group of propositions formulated to explain facts or phenomena that has been repeatedly tested and confirmed either through experiment or observation. A model is a concept to explain a process that has not yet been confirmed by testing or observation. A model can become a theory but only after a process of scientific confirmation.

2 Affidavit of Arthur L. Frank, M.D., Ph.D., dated December 20, 2016.


4 51 F.R. 22612 at 5 (June 20, 1986).

5 U.S.E.P.A. Summary of External Peer Review and Public Comments for Asbestos and Disposition for Asbestos Part I: Chrysotile Asbestos at 135, 175 (December 2020). It is notable that the EPA uses the term "model" appropriately understanding its unproven status.


9 Department of Environmental Health Sciences, University of Massachusetts Amherst.


12 Phenotypic trait is an obvious or observable or measurable trait in an organism.


14 Id. at 2.

15 Calabrese, E.J. Comprehensive Assessment, supra, at 6-12.

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Zellmer speaks and writes extensively on products liability law and asbestos litigation. Such writing and presentation on asbestos litigation include subjects such as premises liability, application of statutes of limitations, medical causation, the litigation in historical context, and exclusivity of remedies under workers' compensation.

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Many years later, the EPA also rejected reliance on the atomic bomb data. 

Calabrese, Comprehensive Assessment, supra, at 15-19.

23 Albert, supra, at 21.

24 Albert, supra, at 78.

25 U.S.E.P.A., Comments, supra.

26 Calabrese, Muller, supra, at 3.

27 Others have presented data supporting thresholds for causation of mesothelioma by other types of asbestos. For example, see Ilgren, E.B. and Browne, K. "Asbestos-Related Mesothelioma: Evidence for a Threshold in Animals and Humans." Regulatory Toxicology and Pharmacology Vol. 13 (1991) at 116-132.


31 https://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?session-id=UxsiOY4UsBen0UQ7LkF0H0aUwYZT4xUaQDUR1pi_cBd69YFF129039450?details=&vocabName=IRIS%20Glossary&filterTerm=no-observed-adverse-effect-level&checkedGlossary=false&checkedTerm=false&hasDefinitions=false&filterTerm=no-observed-adverse-effect-level&filterMatchCriteria=Contains


33 This process of lung digestion and fiber counting varies somewhat from laboratory to laboratory. One aspect is important at the outset. Some laboratories weigh the lung tissue before the water is removed while other laboratories remove the water and weigh the tissue dry. Wet means that the lung tissue is heavier and, hence, fewer fibers per gram of tissue. The number of fibers per gram of lung tissue dry versus wet is approximately ten to one.

34 Wagner, C. "Historical Background and Perspectives of Mesothelioma." in Marie-Claude Jaurand and Jean Bignon, editors, The Mesothelial Cell and Mesothelioma. Vol. 78 (1994) at 8. Interestingly, although the number of chrysotile fibers may predominate in the lung, by a calculation of mass, chrysotile will be "far less" than amphiboles.

35 Id. at 10. Wagner measures the content of the lung against the amount of asbestos likely necessary to cause mesothelioma, not against the amount of background asbestos exposure to be found without the effects of occupational or even para-occupational exposure.


41 Albert, supra, at 78.

42 Cox, supra, at 625.