COLUMNS

MARCH 2022

Asbestos

Raising the Bar in Asbestos Litigation

HARRISMARTIN

www.harrismartin.com

COLUMNS

March 2022 • Vol. 22, No. 3

EDITORIAL STAFF

Publisher/Editorial Director
Jeff Andrus

Managing Editor
Kate McGovern Ferriola

Editor
Marcy Kowalchuk

BUSINESS STAFF

Conference Director
Vicki Gilbreath

Circulation Manager
Alison Murphy

CONTRIBUTING EDITOR

Mark G. Zellmer

Editorial Correspondence
Article submissions and news should be forwarded to Kate McGovern Ferriola, Managing Editor, HarrisMartin Publishing. E-mail: kmcgovern@harrismartin.com

HarrisMartin's *COLUMNS–Asbestos* is published monthly by HarrisMartin Publishing LLC
30 Washington Ave., Ste. D-3
Haddonfield, NJ 08033
$975 print & online annual subscription
$595 print & online 6-month subscription

Questions or subscription requests can be directed to **service@harrismartin.com** or call **(610) 647-5500**.

Advertising Sales
Questions or interest in advertising in *COLUMNS–Asbestos* can be directed to Jeff Andrus at (610) 647-5500.

www.harrismartin.com

COMMENTARY

TABLE OF CASES

COURTROOM NEWS

VERDICT REPORT

DOCUMENT

No Validity to No Safe Dose: Part III - Mechanisms of DNA Repair

A Commentary by Mark G. Zellmer of Husch Blackwell LLP
Author bio on page 8

The linear no threshold model of carcinogenesis (LNT) assumes that all exposures to carcinogens, including asbestos, cause irreversible and, hence, cumulative damage to DNA at the lowest possible doses when viewed in proportion to the amount of exposure. The model is the 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 position 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. Parts I and II of this series of articles explored the rather sordid history of the model, critiques and refutations of the model, the lack of a consensus in support of the model, and a contrast of the model with epidemiology on asbestos.

The crux of Part III is that the modern understanding of DNA repair is wholly inconsistent with the 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.[1] Absent validity to the LNT model, there can be no validity to the claim of no safe dose.[2] Because mechanisms of DNA repair correct damage to DNA, thresholds must exist below which carcinogens, including asbestos, will not cause disease; hence, doses are not cumulative in the causation of disease.

Hermann J. Muller Revisited

In the late 1920s, as an Associate Professor at the University of Texas at Austin, Muller applied very high doses of X-rays to Drosophila (fruit flies).[3] Muller chose a particular specie of fruit fly due to its "favorableness . . . for genetic research."[4] The dose of 285 rads was administered at a rate that would be equivalent to 1,000 modern chest X-rays in three-and-a-half minutes or five X-rays per second. The lowest dose in his Nobel Prize research was even six times higher.[5] Muller referred to the effects in print as "truly mutational."[6]

In the 1930s, Lewis Stadler of the University of Missouri hypothesized that Muller's mutations were more "manifestations of massive deletions and various genetic rearrangements" involving multiple genes.[7] Stadler was ultimately vindicated in his view. Muller had used doses so high that his mutation hypothesis was "untenable."[8] Today, it is known that the dose of radiation can be so high and so concentrated in a short time that the mechanisms of DNA repair are overwhelmed.[9] The massive deletions and genetic rearrangements in Muller's work on fruit flies were too much for any DNA repair. Edward Calabrese found material from the AAAS meeting[10] in Nashville in December of 1927 where Muller admitted the possibility that he did not induce gene mutation but rather large-scale DNA deletions and aberrations.[11]

Despite these issues, Muller called his model the Proportionality Rule.[12] For the next fifty years, into the 1970s, the model was essentially all about radiation. That would change.

Enter OSHA and the EPA

In the early 1970s, during the administration of President Richard Nixon, Congress enacted legislation creating the Occupational Safety and Health Administration (OSHA) and the Environmental Protection Agency (EPA). Although the latter was largely a conglomeration of previously separate agencies throughout the federal government, the former was mostly a new creation. Both would be given broad powers to

regulate exposures in the workplace and in the air, land, and water. Such regulated exposures included carcinogens. In fact, one of OSHA's first major regulatory efforts in 1972 was the regulation of asbestos as a carcinogen.[13]

Charged with risk assessment for carcinogens, both OSHA and the EPA searched for a principle or model of carcinogenesis arising from exposures to chemicals and minerals. Although previously applied to radiation, but not chemicals or minerals, LNT seemed that it might fit the bill.

In 1978, OSHA held hearings that addressed numerous issues including cancer risk assessment. Scientists testified in favor of the linear model. Some industry witnesses criticized the LNT concept, but none of the authoritative, particularly academic, critics of the LNT model, testified.[14] Principal at the time among the critics were Hardin Jones and Alexander Grendon. Noting that the multi-stage process necessary for a carcinogen to cause cancer created a period of latency between the exposure and the occurrence of disease, they advanced the concept already suggested by Hermann Druckrey of "dose-latency-and-tumor-incidence."[15] Lower doses lengthened the latency period. With low-dosage exposure, the risk of disease became virtually nil "because the expected lifespan of those exposed is exceeded by the time necessary for low concentrations of altered cells to develop into cancers."[16] At low doses, latency well beyond the human lifetime created a practical threshold. Jones died in early 1978 before he could testify. Grendon never testified and neither did Druckrey. Why is not known. With a clearly one-sided presentation on the subject, OSHA could easily dismiss the dose-latency concept of Grendon and Jones, leaving LNT as an easy alternative.[17]

The EPA was undertaking a similar exercise in risk assessment in the mid- to late-1970s. One of the people taking the lead at the EPA was toxicologist Roy Albert. He explained much about the process and conclusions in his 1994 article in *Critical Reviews of Toxicology*.[18] The EPA did not hold hearings, but, rather, evaluated the matter internally through one or more committees. As reported by Albert, the personnel at the EPA looked to precedent, namely, what other agencies such as the Atomic Energy Commission (AEC) and the Food and Drug Administration had done. In particular, the AEC used the linear non-threshold model for carcinogenic risk.[19] 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."[20]

Roy Albert's speech in 1975 explained more about the LNT model.[21] His view of its application beyond radiation and to asbestos specifically is clear from the sponsor of the speech, the Asbestos Information Association. Consistent with the tenets of LNT, he explained that the effects of carcinogens were "to a large extent irreversible" and that the occurrence of "mutations" causing cancer provided "a strong basis for thinking that there are no thresholds of effect for carcinogens."[22]

At the same time, Roy Albert's published views with his co-author Bernard Altshuler had a ring of consistency with those of Druckrey, as well as Grendon and Jones. Albert and Altshuler cited Druckrey for the proposition that "the higher the level of the carcinogen exposure the earlier the appearance of tumors."[23] In their article, they made risk estimates of excess disease for people ages 82-83 or younger exposed to carcinogens.[24] They did not explicitly address the reverse view that low dose exposures could lead to cancer only at a time well beyond the normal lifespan.

So, the question remains: on what scientific basis did Roy Albert and the EPA adopt the LNT model of carcinogenesis? Once again, Albert provided the answer in 1994 — it was "extremely simple to use."[25] With a blush of candor, Albert stated that the application of LNT only

"For too long, through the disproven assumptions of LNT, plaintiffs have shifted the burden of proof to defendants. They say that every exposure counts and that there is no safe dose, making every exposure allegedly meaningful to legal causation. Such mantras have no scientific validity and do not belong in a court of law. Without those invalid concepts, plaintiffs are left with the very real burden of proving causation: that the exposure in fact caused the disease."

This is the unfortunate irony: at the very time that OSHA and the EPA were assuming the irreversibility of DNA damage and applying LNT to their risk assessments, science was beginning to understand that damage to DNA was not for an entire human lifetime and that cells have ability to repair damaged DNA. ”

required the lowest data point, a straight edge to draw a line, and some arithmetic. Almost with an air of intellectual honesty, he tried not to overstate the model's scientific validity; rather, in his words, the model had "some biological plausibility"[26] (*emphasis added*). He presented the reasoning that cancer is caused by mutations from genetic damage, that radiation in micro-organisms is known to cause mutations consistent with in a linear model, and that causation of cancer could thereby be expressed with linearity. With such reasoning, Albert admitted that the EPA literally "waved aside" any difference between radiation and chemical carcinogens.[27]

Neither the EPA nor OSHA performed any experiments, testing, or studies to confirm that the LNT model, previously applied to radiation (an erroneous application in any case) could be equally and accurately applied to chemical or mineral carcinogens such as asbestos. The agencies accepted the LNT model for all carcinogens essentially as an article of faith that merely assumed that carcinogenic damage to DNA was irreversible and thereby cumulative.

Discovery of DNA Repair and Its Mechanisms

This is the unfortunate irony: at the very time that OSHA and the EPA were assuming the irreversibility of DNA damage and applying LNT to their risk assessments, science was beginning to understand that damage to DNA was not for an entire human lifetime and that cells have ability to repair damaged DNA.

Today, DNA repair is a well-known phenomenon. In fact, science has revealed multiple mechanisms of DNA repair. Those first discovered and best known are base excision repair (BER), mismatch repair (MMR), and nucleotide excision repair (NER).[28] Other similar, complex terms have been used to describe other mechanisms of DNA repair: single strand break repair (SSBR), double strand break repair (DSBR), and inter-strand cross-link repair (ICLR).[29] That such functions of DNA repair protect against the effects of carcinogens is beyond dispute. As humans — in fact, all living organisms – – are exposed to many sorts of environmental insults damaging to DNA, "robust" repair mechanisms "faithfully" protect DNA.[30] Interestingly, radiation therapy is intended to destroy cancer cells and depends upon the ability of normal cells to repair themselves.[31] 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."[32]

At least, by inference, the evidence of DNA repair was always available in the radiation data. Lewis Stadler demonstrated no excess mutations at the lowest three of 13 doses of radiation to barley.[33] Ernst Caspari's work with fruit flies as part of the Manhattan Project showed a threshold dose for radiation.[34] This and other data were inconsistent with the precept of irreversible genetic damage at the lowest possible dose. If radiation caused genetic damage at low doses, the damage then must be subject to repair. When in the late 1950s William Russell irradiated spermatogonia and oocytes, he found that mutational damage was not cumulative and could be reversible. These findings suggested to him that "DNA-repair must occur even though it had not yet been discovered."[35]

In the early to mid-1960s, Jane Setlow, Richard Setlow, and William Carrier studied UV-irradiated bacterium to discover lesions to DNA called thymine dimers and further found that these lesions were subject to excision from the DNA. Although the mechanism was yet unknown, this function would later be called nucleotide excision repair. During the 1970s, to determine the mechanism of the excision found by the Setlows and Carrier, scientists attempted the identification of the proteins involved in this repair function. In 1983, Aziz Sancar published his discovery of the three proteins that specifically repaired the damage to DNA identified in the earlier research of Setlow and Carrier.[36]

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.[37]

Introduction of an incorrect nucleotide can distort the double strand of DNA. Mismatch repair corrects the error. In 1983, Paul Modrich developed an assay for the analysis of DNA mismatch repair. Then, in 1989, he published his work recreating DNA mismatch repair *in vitro*. In the early 2000s, research by Modrich and others demonstrated the occurrence, mechanism, and effect of mismatch repair in mammalian cells.[38]

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 Sancar, Lindahl, and Modrich.[39]

In 2016, along with his co-author, Jiadong Wang, Lindahl explained the need for and benefits of DNA repair:

> It was ever thought that genomic information is transmitted faithfully from generation to generation. But our current knowledge does not indicate that it is the case. . . Natural decay of DNA molecules is also a fundamental source of changing genomic information. . . Increasing experimental evidence indicates that genomic instability is probably the fundamental reason for carcinogenesis.[40]

With this succinct explanation, Wang and Lindahl linked DNA decay and the occurrence of cancer without exposure to carcinogens.[41]

If the mechanisms of DNA repair correct the damage to DNA at some level of exposure, a threshold must exist below which there is no risk of disease. In fact, any DNA damage from small doses occurring over a long period of time can be repeatedly repaired preventing the occurrence of cancer. The doses are then certainly not cumulative in the causation of disease. If the regulatory agencies had followed the science of DNA repair as it developed, those agencies should have seriously questioned their reliance on the LNT model for risk assessment.

Asbestos and Inflammation

The older view of the pathogenesis of mesothelioma posited that asbestos penetrated the mesothelial cell causing genetic damage, which led to the uncontrolled cellular proliferation of mesothelioma. More recent work has shown that human mesothelial cells invariably die 2-10 days after exposure. Considering the long latency of mesothelioma, cells that die a short time after exposure cannot become malignant cells 20-50 years later. The answer is the occurrence of chronic inflammation due to the exposure to asbestos.[42] A sufficient dose of asbestos, depending on type and fiber dimension, will cause oxidant creation and thereby chronic inflammation.[43] If sustained long enough and severely enough, the inflammation will cause damage to DNA that is irreparable.[44]

Some have refused to accept chronic inflammation as an intermediate step leading to genetic damage and mesothelioma. An example is Dr. Arnold Brody: "Just which genotoxic mechanisms, i.e., DNA binding to asbestos, ROS activation or other undefined mechanisms related to inflammation, are at play in any given tumor remain under active investigation at this time."[45] It may not matter because both genotoxic and non-genotoxic carcinogens have thresholds. According to Takehiko Nohmi of the Biological Safety Research Center in Japan:

> "Recently, however, the nonthreshold discipline for genotoxic carcinogens has been challenged by experimental and theoretical approaches. In fact, this discipline is counterintuitive because humans possess many defense systems against genotoxic chemicals."[46]

And yet, it may matter a lot. Cells normally produce reactive oxygen species (ROS). 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.[47] "Presently, more than 100 oxidative lesions damaging to DNA have been discovered. Most of these are corrected by base excision repair."[48] In 2017, the National Institute for Occupational Safety and Health (NIOSH) caught up with science. At least for carcinogens 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."[49]

Misplaced Reliance on Erroneous Claims Based on LNT

In 2021, the South Carolina Court of Appeals rendered its decision in *Jolly v. General Electric Company*.[50] From 1980 to 1984, Mr. Jolly worked at Duke Power and claimed, among other things, exposure to asbestos from various gaskets used in connection with valves. The jury rendered a verdict for plaintiff and defendant manufacturers appealed. The appellate court affirmed.

Among plaintiff's experts was Dr. Arthur Frank. The appellate court noted his testimony at some length. Dr. Frank testified that "every 'occupational, para-occupational, environmental, or domestic exposure contributes to the risk of developing mesothelioma' and the cumulative exposure contributes to the total dose of asbestos." Dr. Frank stressed that increasing cumulative exposure increases the risk of mesothelioma. All exposures contribute to cumulative dose. It is the cumulative dose of all exposures that causes the disease. To strengthen his position before the Court, he cited agreement to his opinions from the International Agency for Research on Cancer, the Agency for Toxic Substances and Disease Registries, and the National Institute for Occupational Health and Safety. Dr. Frank opined that exposure as low as the current permissible exposure limit of 0.1 f/cc over the course of a year can cause cancer. The South Carolina Court was also swayed by the reasoning of the Pennsylvania Supreme Court in *Rost v. Ford Motor Co*.[51] that it is "irrefutable scientific fact" that "every exposure cumulatively contributes to the total dose (which in turn increases the likelihood of disease)."[52] This reasoning in support of plaintiff's verdict was simply the language of the LNT model. All doses add to a cumulative dose that creates the cumulative risk. There is no dose that does not count.

These statements are simply not accurate. They are fiction. If a dose fails to cause DNA damage, it cannot contribute to the cause of cancer. If a dose causes DNA damage but mechanisms of DNA repair eliminate the damage, it cannot contribute to cause cancer. The concept that each dose contributes to add to cumulative dose and thereby the risk of disease works only if each dose creates damage to DNA that is not reversible, but damage to DNA is reversible.

This inherent rejection of a threshold dose below which there is no risk arises from the LNT model, but the model is specious, not science, and literally a set of disproven assumptions. Dr. Frank's citation to NIOSH is suspect at best. Contrary to the LNT model, NIOSH has recognized the plausibility of thresholds for carcinogens like asbestos causing DNA damage through inflammation. Even the suggestion that a cumulative exposure of 0.1 f/cc-year can cause cancer is a fallacious assumption based upon LNT. That statement comes directly from OSHA's calculation of the risk from such amount of exposure by application of the erroneous assumptions of the LNT model.[53] Studies have shown that calculations of such risk numbers based upon LNT are as much as 150 times too high.[54]

Conclusion: A Word on the Burden of Proof

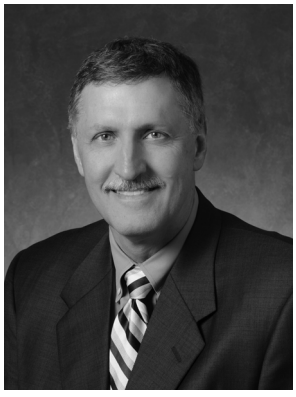
For too long, through the disproven assumptions of LNT, plaintiffs have shifted the burden of proof to defendants. They say that every exposure counts and that there is no safe dose, making every exposure allegedly meaningful to legal causation. Such mantras have no scientific validity and do not belong in a court of law. Without those invalid concepts, plaintiffs are left with the very real burden of proving causation: that the exposure in fact caused the disease.

Endnotes

[1] There are other defense mechanisms to the occurrence of carcinogenesis, including 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. This article simply focuses on DNA repair.

[2] Any exposition on this subject would not be appropriate without mention of the thorough and insightful work of Edward J. Calabrese which will be cited often in this article. His

Mark G. Zellmer is a Partner in the St. Louis, Missouri, office of Husch Blackwell LLP. He is admitted to practice in Missouri (1982) and Illinois (1978) as well as in federal courts in those states. Zellmer earned his J.D. from Saint Louis University School of Law (1978). He earned his B.A. from the University of Notre Dame (1975).



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.

Zellmer defends toxic tort cases, particularly relating to asbestos, as well as other substances and chemicals. Zellmer also defends various defendants in product liability regarding vehicular and industrial equipment. Zellmer's trial practice is active in state and federal courts from coast to coast, and he has acted as national counsel in asbestos litigation.

historical and scientific analysis have laid bare the invalid underpinnings of LNT.

[3] 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 7.

[4] Muller, H.J. "Artificial Transmutation of the Gene." Science Vol. 66, Number 1699 (1927) at 84.

[5] Calabrese (2019), *supra*. at 8.

[6] Muller, *supra*.

[7] Calabrese (2019), *supra*.

[8] Calabrese (2019), *supra*. at 9.

[9] Kanakoglou, D.S. et al. "Effects of High-Dose Radiation in Human Gene Expression: A Meta-Analysis." *International Journal of Molecular Science*. Vol. 21, Number 6 (2020) at 1938.

[10] American Association for the Advancement of Science

[11] Calabrese (2019), *supra*. at 6, footnote 1.

[12] 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 7.

[13] Federal Register: Volume 37, Number 110. June 7, 1972. Part 1: Occupational Health and Safety Title 29- Labor Ch. XVII. ("No one has disputed that exposure to asbestos of high enough intensity and long enough duration is causally related to asbestosis and cancers.")

[14] Calabrese, E. J. et al. "Thresholds for Carcinogens." *Chemico-Biological Interactions*. 341 (2021) at 109464.

[15] *Id*.

[16] Jones, H.B. and Grendon, A. "Environmental Factors in the Origin of Cancer and Estimate of the Possible Hazard to Man." *Food and Cosmetics Toxicology*. Vol. 13, Issue 2 (1975) at 251.

[17] Calabrese (2021) *supra*.

[18] Albert, R.E. "Carcinogen Risk Assessment in the U.S. Environmental Protection Agency." *Critical Reviews in Toxicology*. Vol. 24(1) (1994) at 75.

[19] *Id*. at 78.

[20] *Id*. at 80.

[21] Asbestos Information Association, Second Annual Conference (September 10-11, 1975).

[22] *Id*. at 4, 10.

[23] Albert, R.E. and Altshuler, B. "Assessment of Environmental Carcinogen Risks in Terms of Life Shortening." *Environmental Health Perspectives,* Vol 13 (1976) at 91, 92.

[24] *Id*. at 94.

[25] Albert (1994) *supra*. at 76.

[26] *Id*.

[27] *Id*.

[28] Golden, *supra*. at 4.

[29] 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.

[30] *Id*. at 1.

[31] Kanakoglou, *supra*.

[32] Golden, *supra*. at 4.

[33] Calabrese (2019) *supra*. at 8. Calabrese writes: "While these two titans (i.e., Muller and Stadler) of radiation genetics were unrelenting in their debates (since the stakes were so high) Muller would temporarily prevail (as 'validated' by his Nobel Prize in 1946), possibly due to the power of his personality, and that he outlived Stadler who struggled with cancer over the last eight years of his life. However, once molecular techniques had advanced following the deaths of Muller and Stadler, the data would clearly reveal that Stadler's views were largely vindicated." (Citations omitted) *Id*. at 9.

[34] Calabrese (2019) *supra*. at 11. Kurt Stern, superior of Caspari and friend of Muller, largely deflected and suppressed the Caspari results. Muller had possession of the Caspari data when he gave his speech accepting the 1946 Nobel Prize and lauding LNT, but never mentioned Caspari's results. "Misleading" and "deceptive" are fair terms to describe Muller's speech. *Id*. at 11-12.

[35] Calabrese (2019) *supra*. at 16.

[36] Gustafsson, C. Scientific Background on the Nobel Prize: Mechanistic Studies of DNA Repair. (Kungl Vetenskaps-Akademien, 2015) at 2-3.

[37] Gustafsson, *supra*. at 6-7. Lindahl's findings about the instability of DNA show that persons with problematic DNA repair mechanisms can and will get cancer regardless of their exposure to environmental carcinogens. These are cancers that Tomasetti and Vogelstein would include in cancers resulting from heredity. Tomasetti, C. and Vogelstein, B. "Stem Cell Division, Somatic Mutations, Cancer Etiology, and Cancer Prevention." *Science*. Vol. 355 (2017) at 1330.

[38] Gustafsson, *supra*. at 9-10.

[39] Gustafsson, *supra*.

[40] Wang, J. and Lindahl, T. "Maintenance of Genome Stability." *Genomics Proteomics Bioinformatics.* Vol. 14 (2016) at 119.

[41] There is no reason that mesothelial cells are somehow unique and not subject to the effects of DNA decay leading to cancer.

[42] Carbone, M. et al. "Mesothelioma: Scientific Clues for Prevention, Diagnosis, and Therapy." *CA: A Cancer Journal to Clinicians.* Vol. 69 (2019) at 402, 406. Kuroda, A. "Recent Progress and Perspectives on the Mechanisms Underlying Asbestos Toxicity." *Genes and Environment*. Vol. 43:46 (2021) at 1, 2.

[43] *Id*. 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.

[44] 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.

[45] Brody, A. "How Inhaled Asbestos Causes Scarring and Cancer." *Current Respiratory Medicine Reviews*. Vol. 14 (2018) at 204, 214.

[46] Nohmi, T. and Fukushima, S. *Thresholds for Carcinogens: From Mechanisms to Regulation*. (Academic Press, Amsterdam: 2021) at xiii.

[47] 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.

[48] Gustafsson, *supra*. at 8.

[49] 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.

[50] Appellate Case No. 2017-002611 (2021).

[51] 151 A.2d 1032 (Pa. 2016)

[52] *Id*. Dr. Frank opined and the Court cited that there is "no known safe dose" of asbestos. Although regulatory agencies and other organizations certainly have made such a statement, it should have no part in a trial. The statement does not deny the existence of a safe dose, just that is has not been determined. If there is in fact a threshold, a safe dose, and it is not known, plaintiff cannot prove that it has been exceeded. As mentioned in Part II of this series of articles, plaintiffs that use such statements are trying to avoid their burden of proof and recover for what is not known.

[53] The OSHA dose response equation for mesothelioma per 100,000 people exposed is the following:

Asbestos fibers/cc-years	Mesothelioma
0.1	6.9
0.2	13.8
0.5	34.6
1.0	68
2.0	138
4.0	275

https://www.federalregister.gov/documents/2005/07/29/05-14510/asbestos-exposure-limit. Consistent with LNT, the equation is linear without a threshold.

[54] Camus, M. et al. "Risk of Mesothelioma Among Women Living Near Chrysotile Mines Versus EPA Asbestos Risk Model: Preliminary Findings." *Annals of Occupational Hygiene*. VoI. 46, Supp. 1 (2002) at 95, 98.