Science and Safety

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Perrin Conferences
Talc Litigation Conference

SCIENCE AND SAFETY

May 29, 2024

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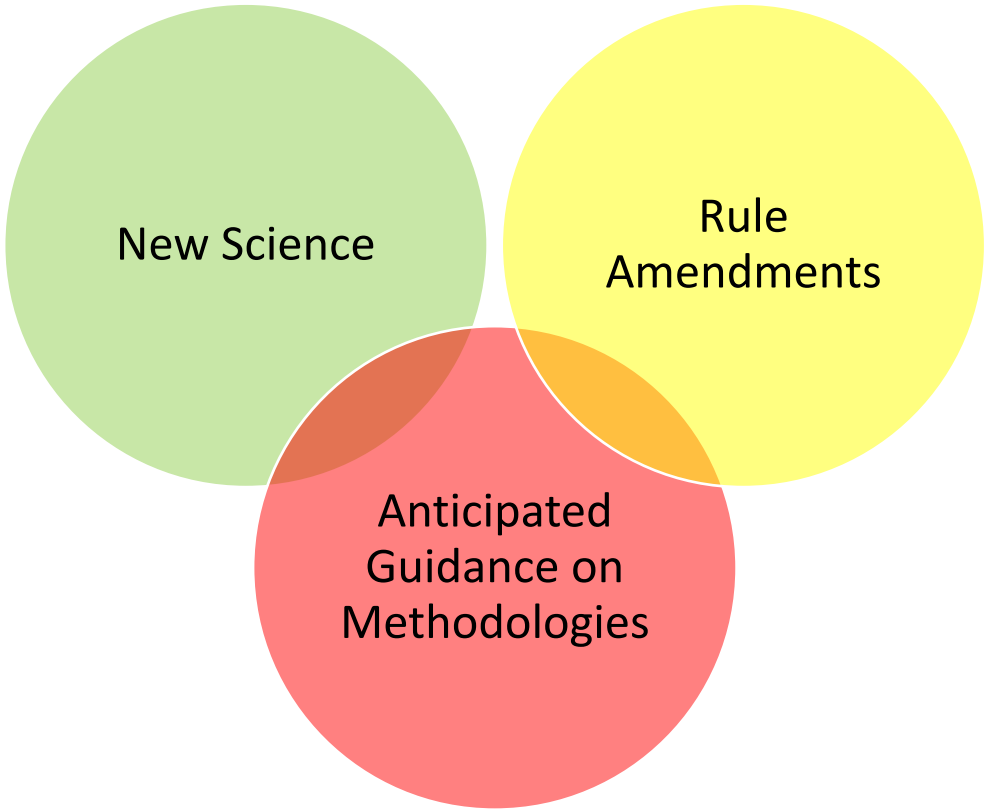
EVOLVING SCIENCE: WHAT'S NEXT?

How do litigants and courts navigate new science, amendments to rules, and anticipated guidance on methodologies?



Talc: Recent Scientific Literature and Data

Emily Goswami, MS, CIH
Technical Director
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Exposure Studies

- Holton et al. (2022): Use of facial makeup
  - Products: Eye shadow, blush, compact powder, contour palette
  - 5/54 air samples contained tremolite
  - 24-hour TWA = 0.00008 f/cc
- Finkelstein (2022): Letter to editor
  - Did not disclose talc source or asbestos concentrations

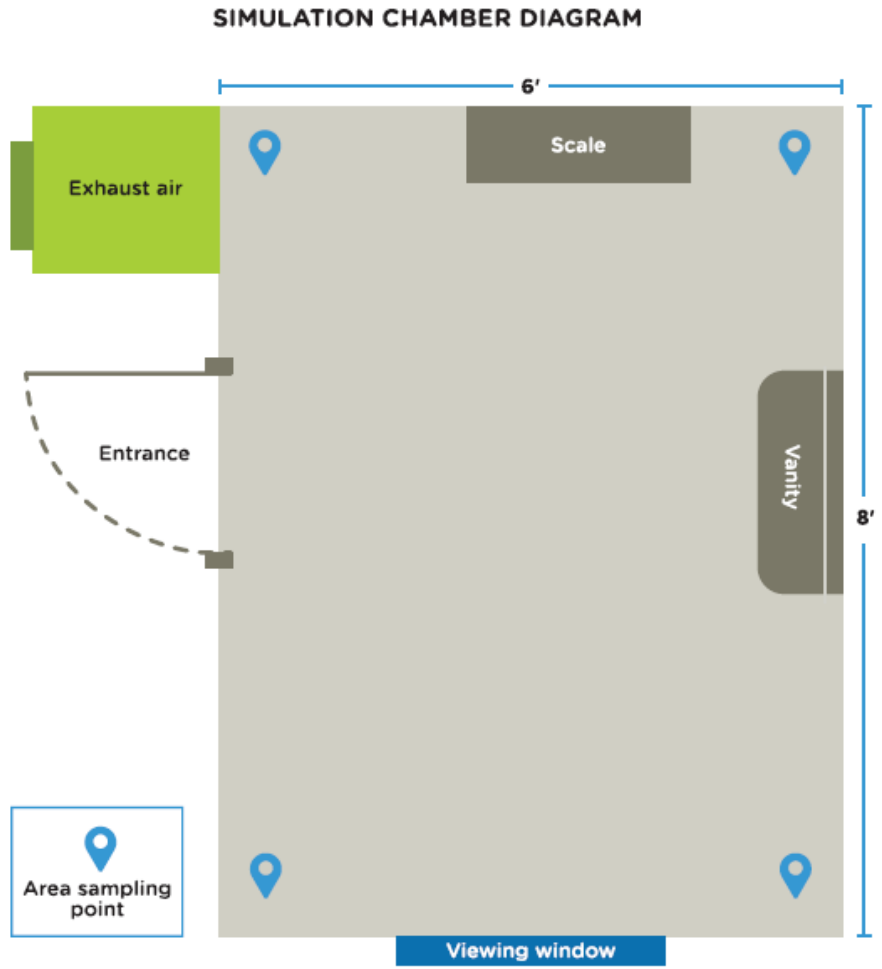
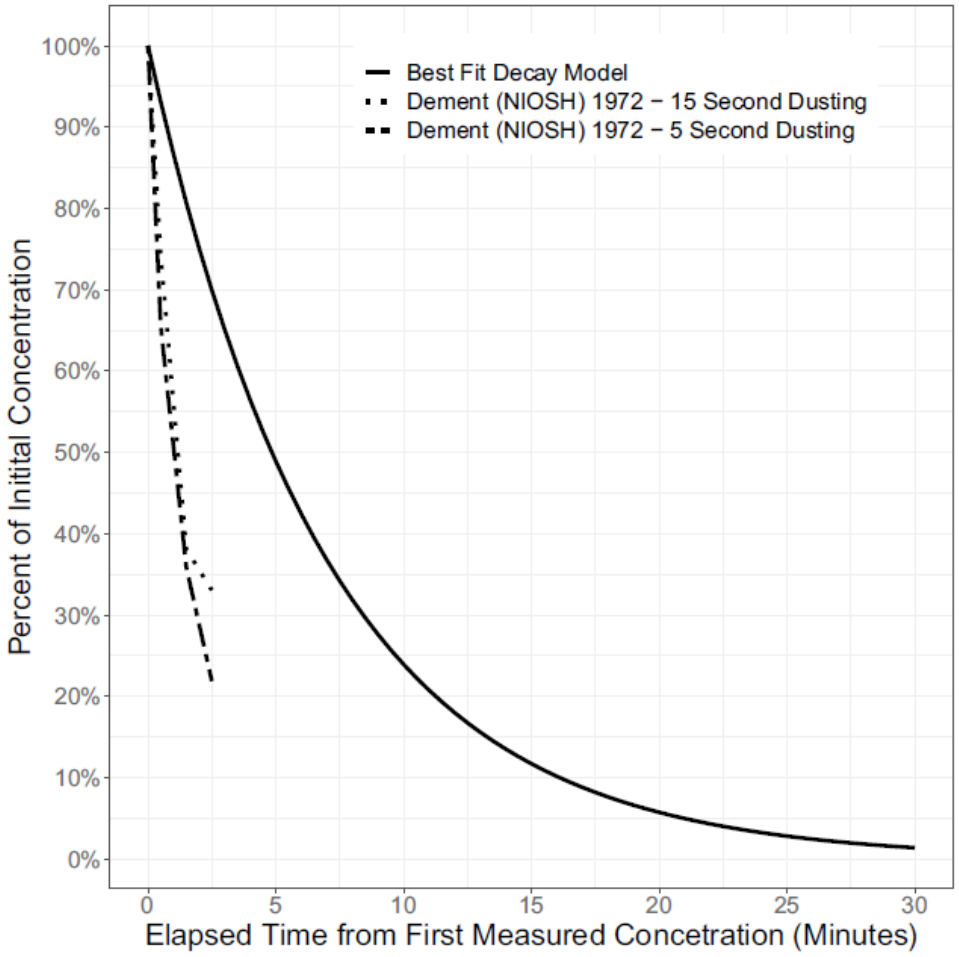


FIGURE 1 Schematic of simulation chamber

Source: Holton et al. 2022

Exposure Studies

- Miller et al. (2022): Use of spiked body powder
  - 0.005 and 0.01% tremolite
  - 0.016 f/cc during first 15 min
  - 0.002-0.004 f/cc next 15 min
- Miller et al. (2024): Modeled exposures using exponential decay
  - “Worst case” exposures 0.006 f/cc over 30 min



Source: Miller et al. 2024

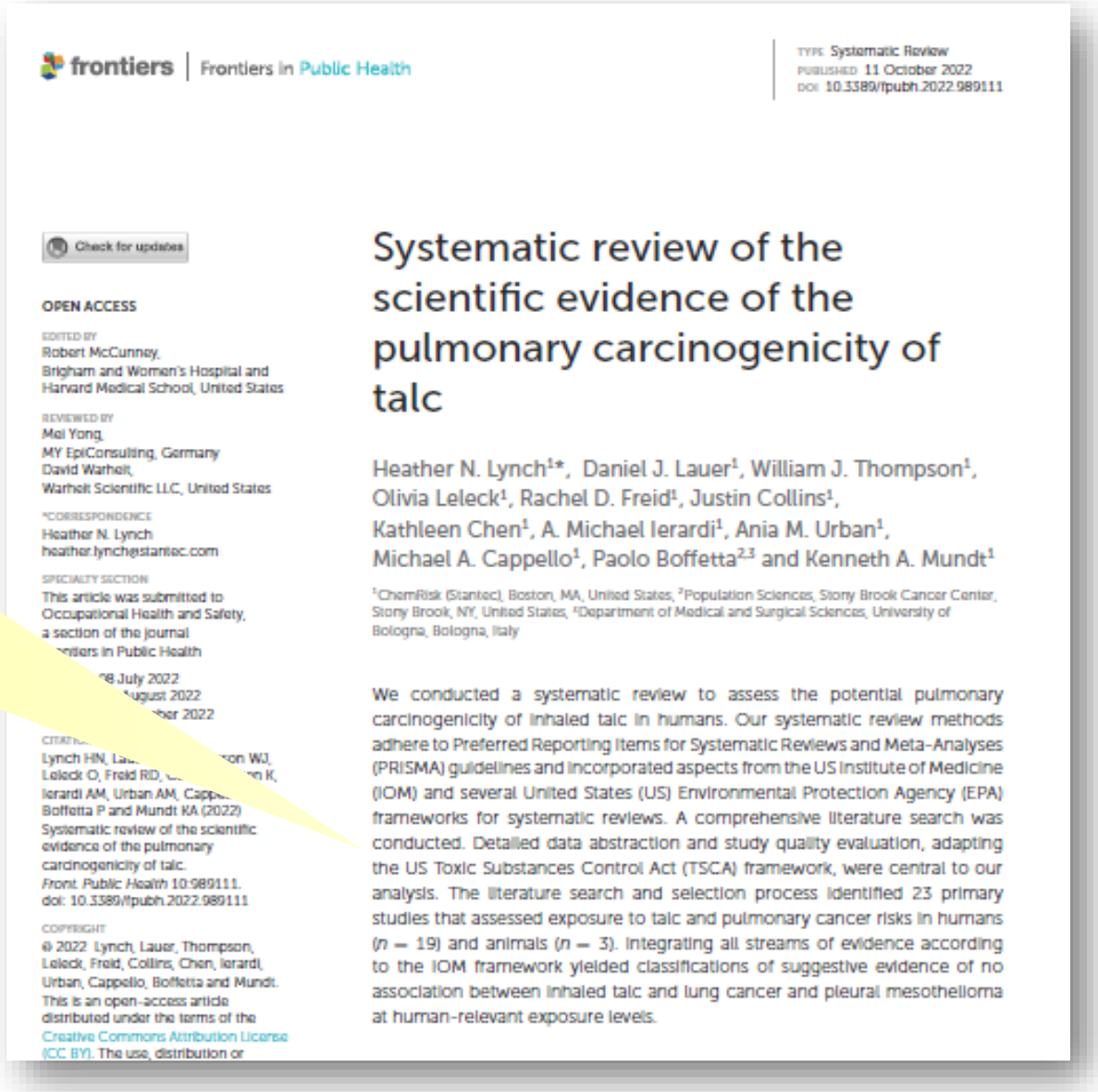
Epidemiology

- Ciocan et al. (2022): Update to mortality study of talc miners and millers
  - Val Chisone, Italy
  - Asbestos was not detected
  - Mortality analyzed 1946-2020 (74 years)

Cause of Death	SMR	95% CI
Mesothelioma	Zero cases	
Lung Cancer	1.02	0.82-1.27
Pneumoconiosis	9.55	7.43-12.08

Review Article: Talc and Cancer

"…no association between inhaled talc and lung cancer and pleural mesothelioma at human-relevant exposure levels."



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Lynch HN, La... on WJ, Leleck O, Freid RD, ... n K, Ierardi AM, Urban AM, Cappello MA, Boffetta P and Mundt KA (2022) Systematic review of the scientific evidence of the pulmonary carcinogenicity of talc. *Front. Public Health* 10:989111. doi: 10.3389/fpubh.2022.989111

Systematic review of the scientific evidence of the pulmonary carcinogenicity of talc

Heather N. Lynch[1]*, Daniel J. Lauer[1], William J. Thompson[1], Olivia Leleck[1], Rachel D. Freid[1], Justin Collins[1], Kathleen Chen[1], A. Michael Ierardi[1], Ania M. Urban[1], Michael A. Cappello[1], Paolo Boffetta[2,3] and Kenneth A. Mundt[1]

[1]ChemRisk (Stantec), Boston, MA, United States, [2]Population Sciences, Stony Brook Cancer Center, Stony Brook, NY, United States, [3]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

We conducted a systematic review to assess the potential pulmonary carcinogenicity of inhaled talc in humans. Our systematic review methods adhere to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and incorporated aspects from the US Institute of Medicine (IOM) and several United States (US) Environmental Protection Agency (EPA) frameworks for systematic reviews. A comprehensive literature search was conducted. Detailed data abstraction and study quality evaluation, adapting the US Toxic Substances Control Act (TSCA) framework, were central to our analysis. The literature search and selection process identified 23 primary studies that assessed exposure to talc and pulmonary cancer risks in humans (n = 19) and animals (n = 3). Integrating all streams of evidence according to the IOM framework yielded classifications of suggestive evidence of no association between inhaled talc and lung cancer and pleural mesothelioma at human-relevant exposure levels.

Review Article: Mesothelioma and Occupational Exposure to Cosmetic Talc

"Overall, the epidemiological evidence does not support an increased risk of mesothelioma for these occupations..."

k for updates

Review

Toxicology and Industrial Health

Toxicology and Industrial Health
2023, Vol. 0(0) 1–19

DOI: 10.1177/07482337231191162
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Occupational exposure to cosmetic talc and mesothelioma in barbers, hairdressers, and cosmetologists: A systematic review of the epidemiology

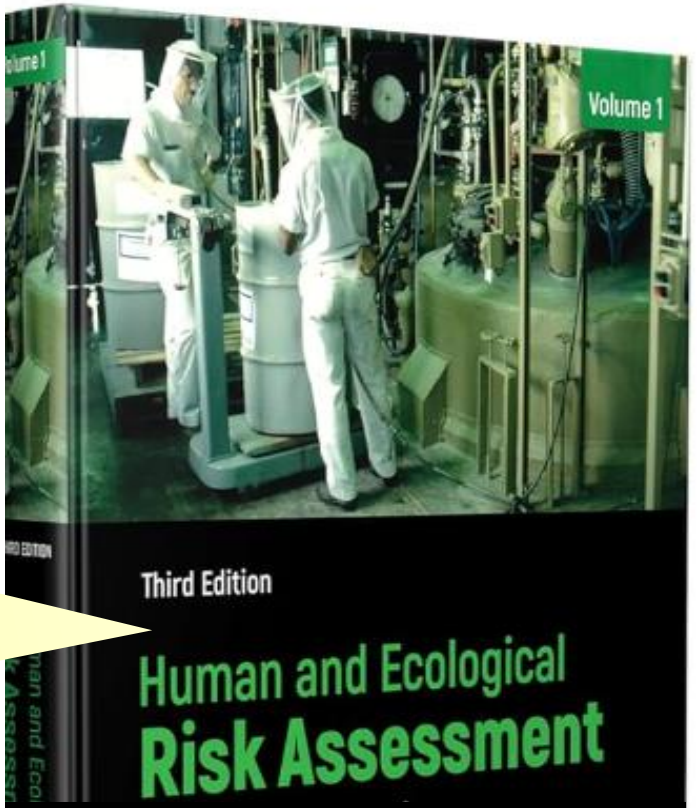
Ryan C Lewis[1], Sierra J Smith[2], Callan F Krevanko[3], Ethan D Hall[4], Eric W Miller[4], Evan M Beckett[5] and Jennifer S Pierce[2]

Abstract

Inhalation exposure to cosmetic talc has generated much scientific debate regarding its potential as a risk factor for mesothelioma, a rare, but fatal cancer. Barbers, hairdressers, and cosmetologists have regularly used cosmetic talc-containing products, but the collective epidemiological evidence for mesothelioma in these occupations has yet to be described. As such, we conducted a systematic review of PubMed and the National Institute for Occupational Safety and Health's (NIOSH) Numbered Publications list to identify original epidemiological literature reporting measures of association between these occupations and incidence of or death from mesothelioma. Literature screening was performed independently twice, the [illegible] which were summarized and tabulated and underwent a review for their accuracy. A total of 12 studies met our inclusion criteria, including three cohort, six case–control, and three proportionate mortality/[illegible]tion studies. The data from these studies were collected in 13 European and North American countries spanning more than 50 years. We supplemented this review with queries of occupational mortality databases that are managed by the Washington State Department of Health and NIOSH for 26 U.S. states. Most findings were null and if statistically significant, nearly all showed an inverse relationship, indicative of a protective effect of these occupations on mesothelioma risk. Overall, the epidemiological evidence does not support an increased risk of mesothelioma for these occupations. This research fills an important data gap on the etiology of mesothelioma in barbers, hairdressers, and cosmetologists, and provides a benchmark for those with comparatively less exposure, such as non-occupational users of similar cosmetic talc-containing products.

Review Article: Cosmetic Talc and Cancer

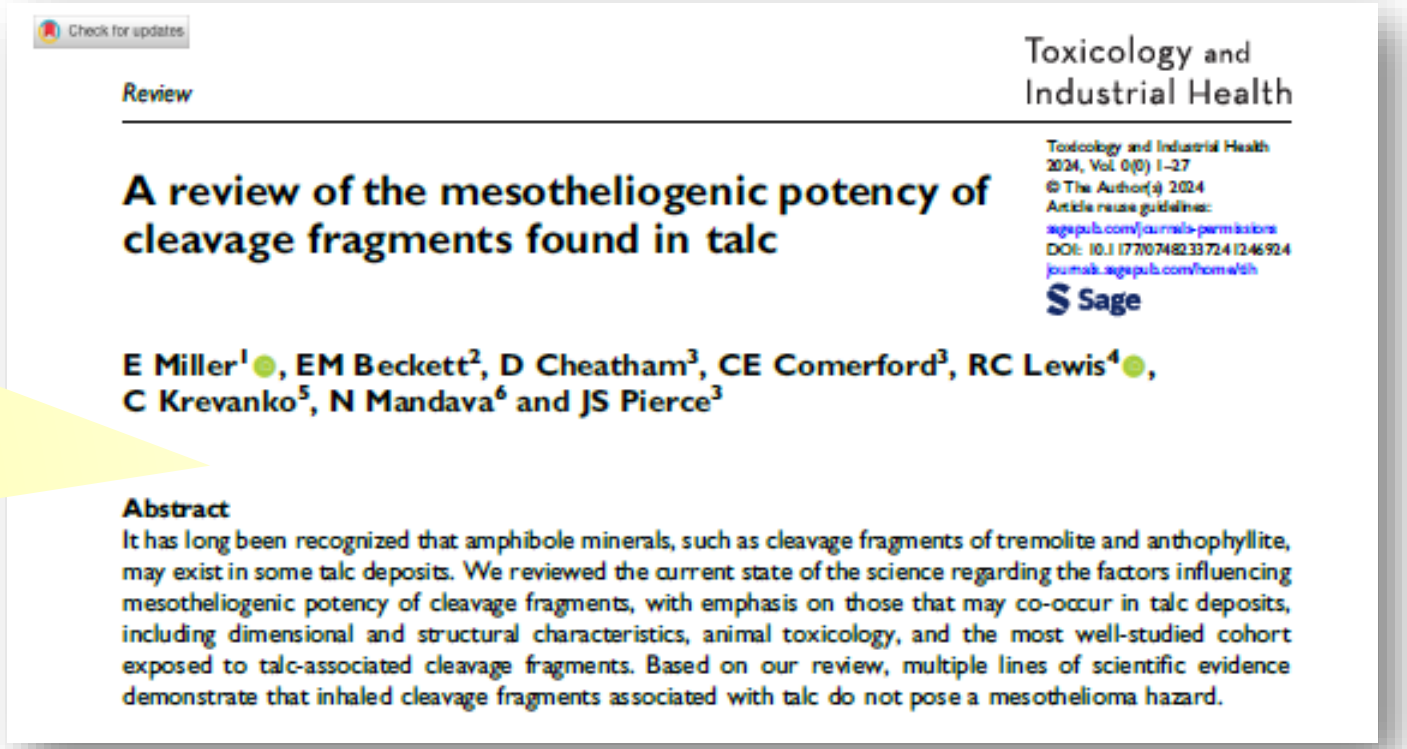
"The current weight of evidence indicates that typical consumer use of cosmetic talc-containing products does not pose a carcinogenic health risk."



Chapter 13: A Risk Assessment of Cosmetic Talc for the Development of Mesothelioma and Ovarian Cancer.
Ierardi, Amanda Burns, Ania Urban, Brent Finley
2024

Review Article: Potency of Cleavage Fragments

"Based on our review, multiple lines of scientific evidence demonstrate that inhaled cleavage fragments associated with talc do not pose a mesothelioma hazard."



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Review

Toxicology and Industrial Health

A review of the mesotheliogenic potency of cleavage fragments found in talc

Toxicology and Industrial Health
2024, Vol. 0(0) 1–27

DOI: 10.1177/07482337241246924
journals.sagepub.com/home/tih
Sage

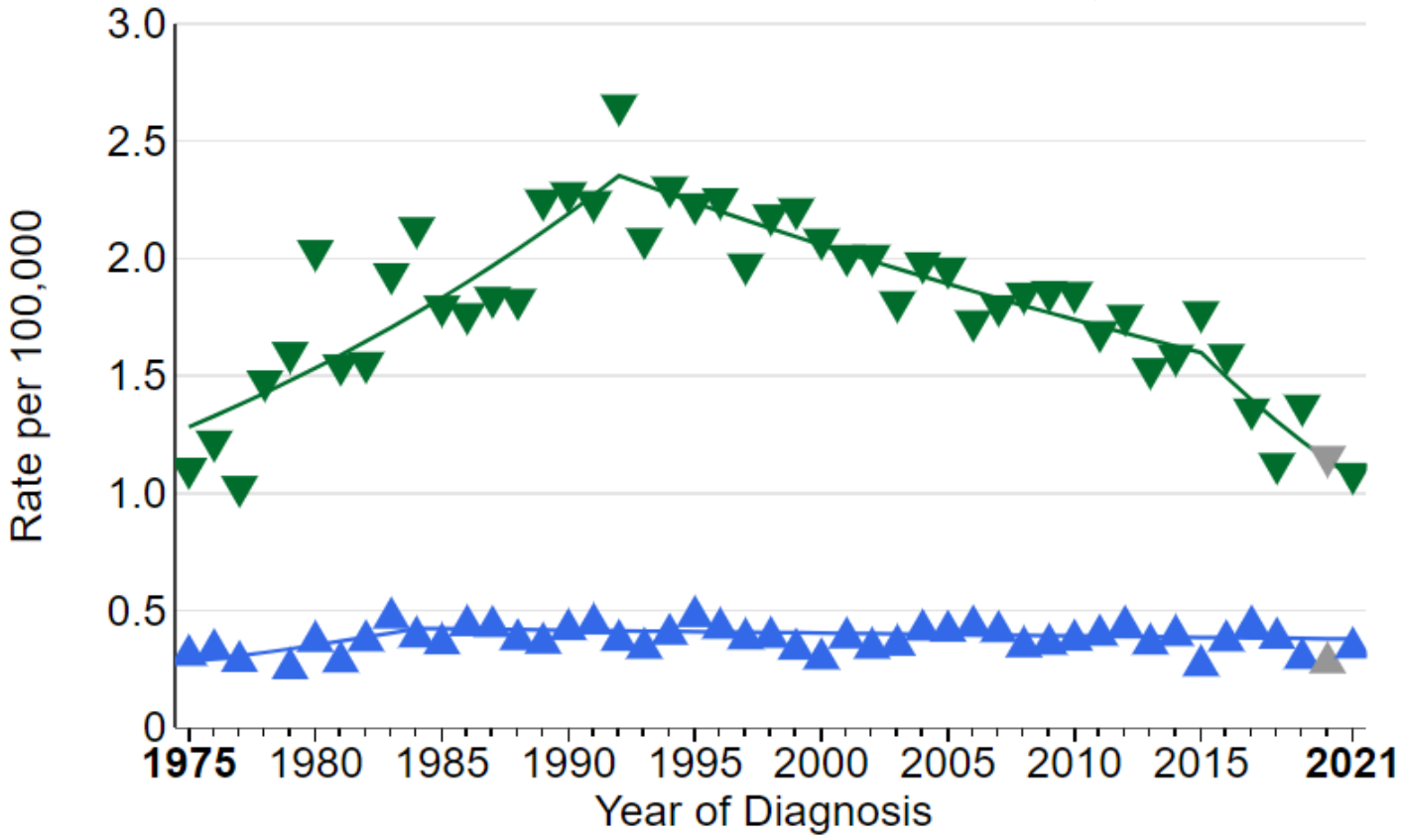
E Miller[1], EM Beckett[2], D Cheatham[3], CE Comerford[3], RC Lewis[4], C Krevanko[5], N Mandava[6] and JS Pierce[3]

Abstract

It has long been recognized that amphibole minerals, such as cleavage fragments of tremolite and anthophyllite, may exist in some talc deposits. We reviewed the current state of the science regarding the factors influencing mesotheliogenic potency of cleavage fragments, with emphasis on those that may co-occur in talc deposits, including dimensional and structural characteristics, animal toxicology, and the most well-studied cohort exposed to talc-associated cleavage fragments. Based on our review, multiple lines of scientific evidence demonstrate that inhaled cleavage fragments associated with talc do not pose a mesothelioma hazard.

SEER Mesothelioma Incidence Data

- Updated through 2021
- Based upon cancer registries in the U.S.



Source: SEER, 2024

Genomics, Asbestos and Talc

Science and Law Update

Kirk T. Hartley
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ToxicoGenomica

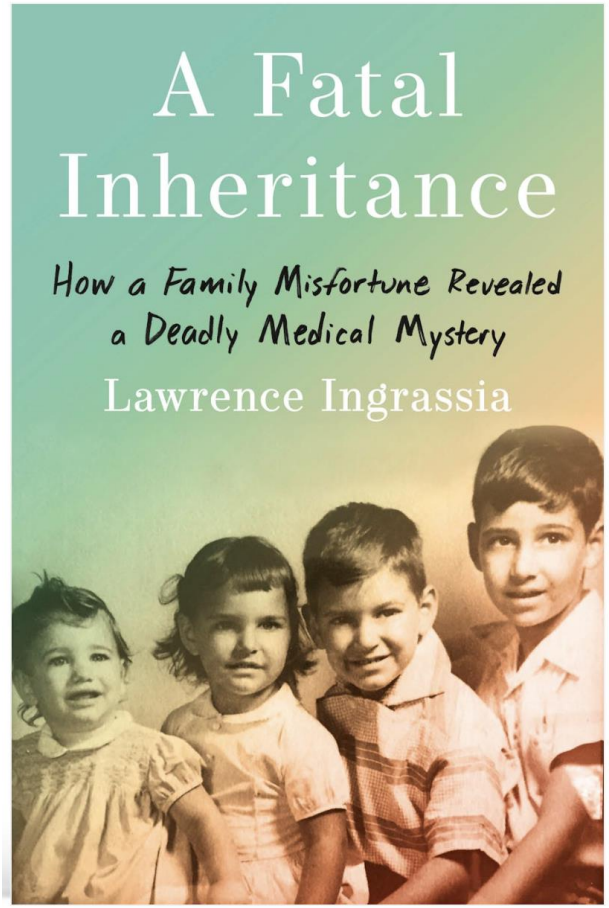
New Book - A Fatal Inheritance – TP53 – Li-Fraumeni Cancer Syndrome

- “It may be hard to imagine a family in America that hasn't been wounded by cancer. The losses in Lawrence Ingrassia's family have been extraordinary. His mother, Regina, died of breast cancer when she was 42. Larry was 15. His sister Angela died about a decade later of abdominal cancer at the age of 24. And his nephew Charlie got cancer in his cheek when he was just 2. His sister Gina was lost to lung cancer when she was 32. And his brother Paul, also then working for The Wall Street Journal, had to contend with several different cancers for more than 20 years.”

- “What did Frederick Li and Joseph Fraumeni develop, uncover, discover, establish that had been missing?

- In 1990, late 1990, they discovered a mutation and a gene that turns out to be hugely important. It's called p53.”

- https://www.npr.org/2024/05/18/1252307797/a-fatal-inheritance-follows-a-familys-struggle-with-cancer-across-generations



Suggested takeaways from A Fatal Inheritance

- Broad studies of family histories and family member tissues were keys to proving the existence of the cancers syndromes now known as Li-Fraumeni and HBOC (Hereditary Breast and Ovarian Cancer), and were keys to developing better anti-cancer therapies
- Today, disease research is heavily based on biobanks that hold medical histories and tissues, ranging from the massive UK biobank (500k whole genomes and tissue) to the ongoing All of US program, to specialized biobanks focused on Li-Fraumeni, HBOC, and mesothelioma
    - See generally Rashid, R., Copelli, S., Silverstein, J. C., & Becich, M. J. (2023). REDCap and the National Mesothelioma Virtual Bank-a scalable and sustainable model for rare disease biorepositories. *Journal of the American Medical Informatics Association : JAMIA*, *30*(10), 1634–1644.
- Litigants and courts can and should encourage or require contribution of cancer lawsuit data to pertinent biobanks
- Personal and family disease histories and genetic data are keys to analyzing disease etiologies
- Some cancer syndromes cause cancers in a wide range of different organs and types of tissues
- Early age of onset often is a key "tell" to the presence of a hereditary cancer syndrome, but late onset cancers and other diseases also arise
- Far too many doctors (most?) know virtually nothing about genetics and hereditary disease syndromes, but nonetheless some will say things that are far outside their actual knowledge

Five year old child - Redzapagic 2024 - pediatric peritoneal mesothelioma: case report with a literature review – open access - May 18, 2024 article

"Our comprehensive literature search on molecular profiling of pediatric peritoneal mesotheliomas revealed only a few studies (summarized in *Table 1).*

Table 1. Overview of genomic features of peritoneal mesotheliomas in the pediatric population

Year	Author	Patients (n)	Age (range)	Location	Molecular assay (method)	Identified genomic alterations (*n*)
2021	Argani *et al.* [18]	5	15 years (mean) (range, 8–16)	Peritoneum and tunica vaginalis testis	FISH, Archer FusionPlex (RNA sequencing) and conventional cytogenetics	*STRN-ALK* fusion ($n = 1$), *ALK-TPM1* ($n = 1$) *ALK* rearrangements ($n = 2$) $t(2;15)$ ($n = 1$)
2021	Murumagi *et al.* [19]	1	5 years	Peritoneum	NGS Foundation One, FISH	*STRN-ALK* fusion
2021	Sakata *et al.* [21]	1	14 years	Peritoneum	NGS	*STRN-ALK* rearrangement
2021	Olmedilla *et al.* [22]	1	12 years	Peritoneum	FISH, NGS (Impact panel)	*TERT* promoter translocation
2021	Ren *et al.* [23]	2	15 years both	Peritoneum and pericardium	RNA sequencing (Illumina TruSight RNA Fusion Panel), FISH	*EWSR1-ATF* fusion (n = 1) *EWSR1* rearrangement ($n = 1$)
2018	Mijalovsky *et al.* [20]	1	4 months	Peritoneum	WES	*ATM mutation*
2016	Loharamtaweethong *et al.* [32]	1	10 years	Peritoneum	FISH	*ALK* translocation
2013	Sugalski *et al.* [10]	1	7 years	Peritoneum	Conventional cytogenetic analysis	trisomy 11, deletion 19q13.33

FISH, Fluorescent In Situ Hybridization; NGS, next-generation sequencing; WES, whole exome sequencing.

Redzepagic, J., Zvizdic, Z., Bilalovic, N., Milisic, E., Bukvic, M., & Vranic, S. (2024). Comprehensive genomic profiling of pediatric peritoneal mesothelioma: case report with a literature review. *Journal of surgical case reports*, *2024*(5), rjae324. https://doi.org/10.1093/jscr/rjae324

More from Redzepagic 2024 re pediatric meso

Genomic analysis is key, and so is thinking beyond the >2,000 BAP1 mutations

- "Therefore, we conducted a comprehensive genomic profiling of [the tumor in] our case, which revealed no somatic mutations including the BAP1 gene (mutated in 85% of peritoneal mesotheliomas and around 30% of pleural mesotheliomas) [17], but amplifications of AURKA, AURKC, HLA-1B, ZNF-217, OR5F1 and MEN1 gene.

- "In organisms, gene amplification may occur through two different mechanisms, planned or unplanned. The former may be a part of the developmental stage of the embryo; the amplification of chorion genes in fruit fly ovaries or the amplification of actin genes during the development of chicken muscle tissues are two examples in this regard."
- "The amplification displayed by mammals is the unplanned aberration which involves two unrelated mechanisms. Unplanned DNA amplification occurs in cellular response during tumor growth or from exposure to cytotoxic agents.[17,18]"

- Bagci O, Kurtgöz S. Amplification of Cellular Oncogenes in Solid Tumors. *N Am J Med Sci*. 2015;7(8):341-346. doi:10.4103/1947-2714.163641

- "Also, AURKA gene alterations were associated with poor prognosis [28]."

- "The AURKA gene could be a potential therapeutic target with AURKA kinase A inhibitors [28]."

- Another relevant finding in our study is the Zinc finger protein 217 (ZNF217) gene amplification. ZNF217 is a transcription factor, involved in cancer initiation and progression [29]. Interestingly, Ugurluer et al. detected ZNF217 mutation as a variant of unknown or additional significance in a small cohort of 11 pleural and peritoneal mesotheliomas [30].

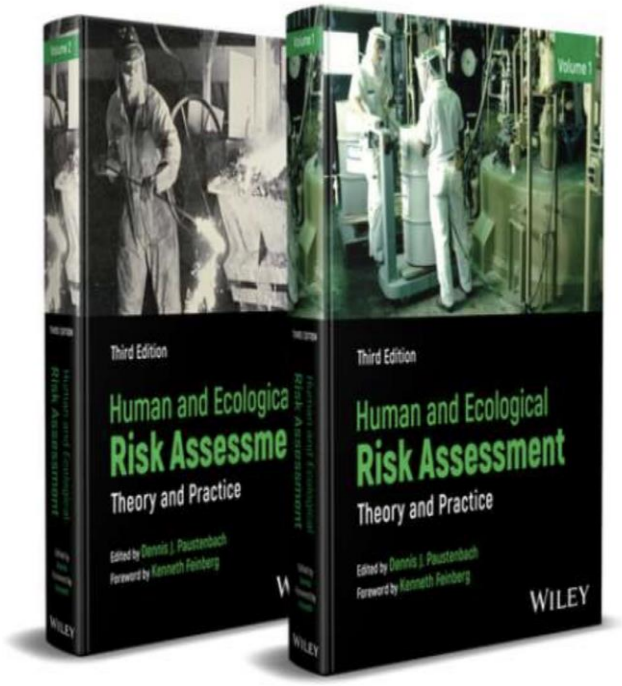
- "Mutation in the MEN1 gene could be related to Multiple endocrine neoplasia syndrome, while OR5F1 alterations have not been reported yet in peritoneal mesotheliomas. "

- "Expression of HLA antigens can determine tumor progression and metastatic potential by influencing the immune response [31]."

New Dennis Paustenbach (Ed.) book with multiple pertinent authors and topics

- Human and Ecological Risk Assessment: Theory and Practice, Set, 3rd Edition. Dennis J. Paustenbach (Editor). ISBN: 978-1-119-74297-5. April 2024. 1312 pages
- Forward by Ken Feinberg
- **"B.5 Case Studies Involving Occupational Exposure 609**
- 16 Assessment of Human Health Risks Associated with Changing Clothes and Handling Work Uniforms Containing Foundry Dust 611
  Jason T. Lotter, Tyler V. Ferracini, Benjamin Roberts, and Thomas J. Slavin
- 17 A Review of Take-Home Exposure and Risk Associated with the Handling of Clothing Contaminated with Asbestos 643
  Tyler V. Ferracini and Jennifer Sahmel

Human and Ecological Risk Assessment, Theory and Practice, Set



New asbestos specific textbook – Carbone, Dodson, Pass and Yang

- 3rd Edition, Asbestos Risk Assessment, Epidemiology, and Health Effects

Edited By Michele Carbone, Ronald F. Dodson, Harvey Pass, Haining Yang

- Order at:
  - https://www.routledge.com/Asbestos-Risk-Assessment-Epidemiology-and-Health-Effects/Carbone-Dodson-Pass-Yang/p/book/9781032521060#

- "Available for pre-order on July 31, 2024. Item will ship after August 21, 2024"

Chapters in new asbestos specific textbook – Carbone, Dodson Pass and Yang

- **1. The History of Asbestos Utilization and Recognition of Asbestos-induced Diseases.**
  Sonja Klebe, James Leigh and Douglas W. Henderson
- **2. Asbestos Analysis Methods.**
  James R. Millette and Steven P. Compton
- **3. Analysis and Relevance of Asbestos/Elongated Particulate Burden in Tissue.**
  Ronald F. Dodson
- **4. Evaluation of Asbestos Exposure.**
  S.D. Visonà, B. Bertoglio, C. Favaron, S. Capella, E. Belluso, C. Bortolotto, A. Marrocco and C. Colosio
- **5. Mechanisms of Asbestos Carcinogenesis.**
  Giovanni Gaudino and Haining Yang
- **6. Epidemiology of Mesothelioma in the World.**
  Emanuela Taioli
- **7. Environmental Exposure to Asbestos and Cancer.**
  Francine Baumann
- **8. Asbestos and Immunity.**
  Yasumitsu Nishimura
- **9. Medical Findings Related to Asbestos Exposure.**
  Yosuke Miyamoto and Nobukazu Fujimoto
- **10. Mesothelioma in 2024: What's New?**
  Lydia Giannakou, Haining Yang and Michele Carbone
- **11. Pathologic Diagnosis of Mesothelioma.**
  David B. Chapel, Aliya N. Husain and Thomas Krausz
- **12. Bioinformatics Approaches to Studying Diffuse Malignant Mesothelioma.**
  Alicia A. Zolondick and Michele C. Carbone
- **13. OncoTherapy in Mesothelioma.**
  Steven G. Gray, Tomer Meirson and Luciano Mutti
- **14. Surgical Management of Mesothelioma.**
  Sara Kryeziu, Harvey I. Pass and Stephanie Chang
- **15. Asbestos Related Cancers.**
  Sara Ricciardi, Delia Giovanniello and Giuseppe Cardillo
- **16. Asbestos Litigation and Trust Funds in the United States.**
  Alan Brayton, Ellen Tenenbaum and Craig Zimmerman

Presentation Overview

- Examples from recent genomics literature
- Objective, reproducible data arises from tumor or germline sequencing
  - VAF %s
  - CADD scores
- Notable recent genetic testing motions and orders
- Notable developments regarding differential etiologies and absence of genetic sequencing data

Biobanks Ramping Up Data – 198 authors , many from major institutions - "Large-scale genome-wide association study of 398,238 women unveils seven novel loci associated with high-grade serous epithelial ovarian cancer risk"

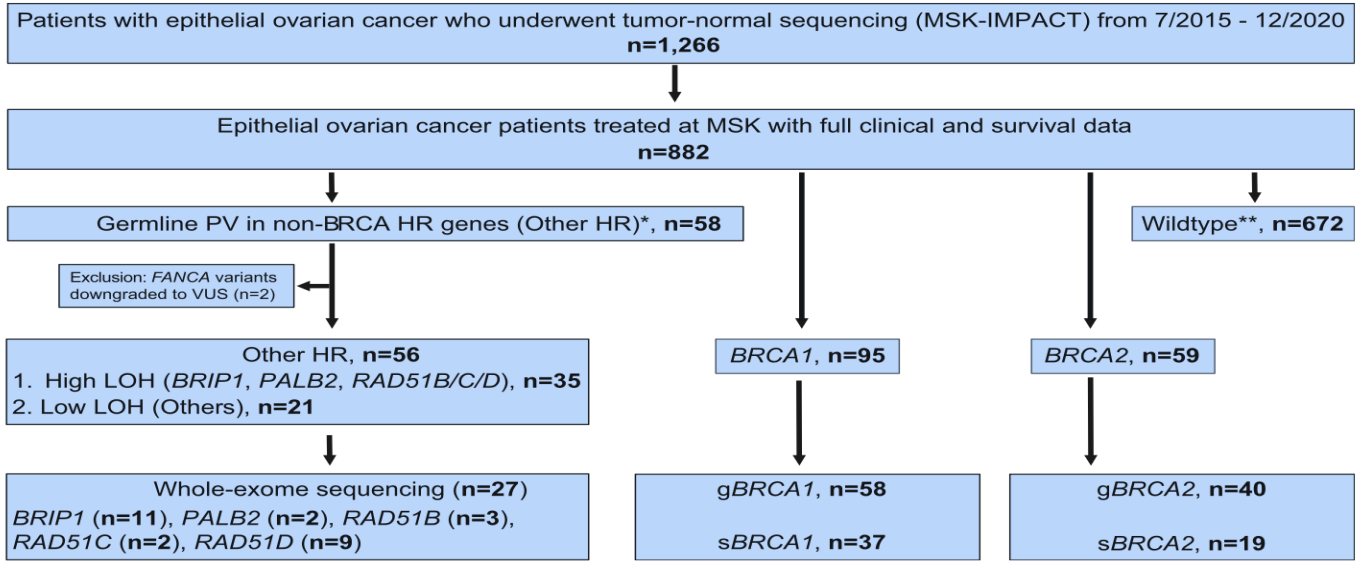
- "We analyzed >22 million variants for 398,238 women."

- "Nineteen genomic regions have been associated with high-grade serous ovarian cancer (HGSOC). We used data from the Ovarian Cancer Association Consortium (OCAC), Consortium of Investigators of Modifiers of *BRCA1/BRCA2* (CIMBA), UK Biobank (UKBB), and FinnGen to identify novel HGSOC susceptibility loci and develop polygenic scores (PGS)."

- "Eight novel variants were associated with HGSOC risk. … This study represents the largest GWAS for HGSOC to date. The results highlight that improvements in imputation reference panels and increased sample sizes can identify HGSOC associated variants that previously went undetected, resulting in improved PGS. The use of updated PGS in cancer risk prediction algorithms will then improve personalized risk prediction for HGSOC."

- Barnes DR, Tyrer JP, Dennis J, et al. Large-scale genome-wide association study of 398,238 women unveils seven novel loci associated with high-grade serous epithelial ovarian cancer risk. Preprint. *medRxiv*. 2024;2024.02.29.24303243. Published 2024 Mar 4. doi:10.1101/2024.02.29.24303243

Kahn 2023 – MSKCC – more data regarding pathogenic germline variants in ovarian cancers



Kahn RM, Selenica P, Boerner T, et al. Pathogenic germline variants in non-BRCA1/2 homologous recombination genes in ovarian cancer: Analysis of tumor phenotype and survival. *Gynecol Oncol*. 2024;180:35-43

Congedo 2024 – 20% estimate for genomic mesotheliomas

- "The incidence of MPM cases without an apparent association with asbestos exposure has been increasing in recent years, suggesting that genetic predisposing factors may play a crucial role."

- "Several candidate genes have been associated with a predisposition to MPM and most of them play a role in DNA repair mechanisms: overall, approximately 20% of MPM cases may be related to genetic predisposition."

- "Germline variants in BAP1 predispose to the development of MPM following an autosomal dominant pattern of inheritance in the familial cases."

- "MPMs in these patients are significantly less aggressive, and patients require a multidisciplinary approach that involves genetic counseling, medical genetics, pathology, surgical, medical, and radiation oncology expertise.

  - Congedo MT, West EC, Evangelista J, et al. The genetic susceptibility in the development of malignant pleural mesothelioma: somatic and germline variants, clinicopathological features and implication in practical medical/surgical care: a narrative review. J Thorac Dis. 2024;16(1):671-687.

Febres-Aldana 2023 – germline variants cause mesothelioma

- Physicians and researchers from Memorial Sloan Kettering Cancer Center (MSKCC) issued a notable fall 2023 article with the following three key statements:

- "Other causes unrelated to asbestos are being more clearly defined including other nonasbestos minerals, germline variants, etc." at 12

- "Moreover, biallelic BAP1 inactivation has been shown to be sufficient to drive the development of nonasbestos-related mesothelioma (85) and is synergistic with loss of NF2 or CDKN2A in inducing mesothelioma in mice (97)." at 19

- "Remarkably, while BAP1 inactivation is oncogenic, not all BAP1-deficient DPMs exhibit poor prognosis. A subset of epithelioid DPMs arising in the context of germline BAP1 mutations is less aggressive, showing significantly improved survival (92)." at 20

- Febres-Aldana, C. A., Fanaroff, R., Offin, M., Zauderer, M. G., Sauter, J. L., Yang, S. R., & Ladanyi, M. (2024). Diffuse Pleural Mesothelioma: Advances in Molecular Pathogenesis, Diagnosis, and Treatment. *Annual review of pathology*, *19*, 11–42.

Lebensohn 2024 – nail abnormalities in carriers of germline BAP1 mutations

- “Among 47 participants …ranging in age from 13 to 72 years from 35 families, nail abnormalities were detected in 41 patients (87.2%) and included leukonychia, splinter hemorrhage, onychoschizia, and distal nail hyperkeratosis. “
- “This study found that BAP1 TPDS was associated with a high rate of nail abnormalities consistent with onychopapillomas in adult carriers of the disease.”
- “Findings suggest that this novel cutaneous sign may facilitate detection of the syndrome in family members who are at risk and patients with cancers associated with BAP1 given that multiple onychopapillomas are uncommon in the general population and may be a distinct clue to the presence of a pathogenic germline variant in the BAP1 gene.”

eFigure 1. Polydactylous onychopapillomas in a female (age 40’s) with BAP1 TPDS.

A. Multiple discrete longitudinal bands with variable leukonychia, erythronychia and splinter hemorrhage on 1st digits of patient with BAP1 TPDS. B. Hyponychial view of nail margin demonstrates subungual columns of hyperkeratotic nail material corresponding to the bands of nail plate discoloration.

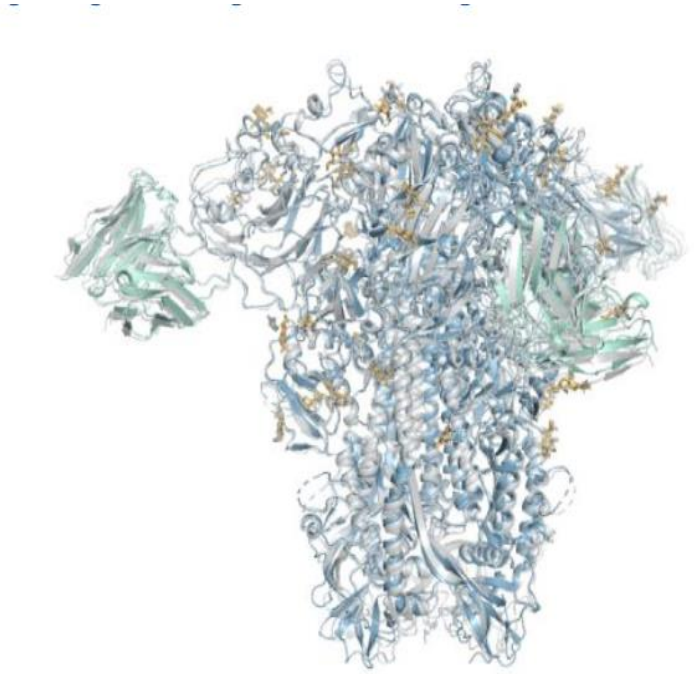
Deep Mind (AI) - predicting protein-protein interactions (May 2024)

- Over time, the knowledge generated by AphaFold3 should allow mass tort stakeholders to understand and show precisely why some combinations of pathogenic mutations (germline or somatic) can and do (or do not) cause some cancers and other diseases.

- Note the increasingly rapid advances in AlphaFold3's ability to predict/show interactions between the genetically driven proteins that are fundamental to health or sickness.

- Per the article: "Now, DeepMind says, AlphaFold 3 can predict the structures of DNA, RNA, and molecules like ligands, which are essential to drug discovery. DeepMind says the tool provides a more nuanced and dynamic portrait of molecule interactions than anything previously available."

- https://www.technologyreview.com/2024/05/08/1092183/google-deepminds-new-alphafold-can-model-a-much-larger-slice-of-biological-life/



Google DeepMind's new AlphaFold can model a much larger slice of biological life

VAF %s – Using Tumor Sequencing Results to Identify Likely Germline Mutations

- "Pathogenic variants are assumed to be of germline origin when the allele frequency is approximately 50%, but a range between 30% and 70% is commonly accepted as representative of a heterozygous pathogenic variant [mutation in one copy of a gene]."
- "In tumor genomic profiling, the higher the variant allele frequency, the more likely the variant is germline." DeLeonardis *et al*., 2019.
- Objective, reproducible, quantitative data generated by sequencing labs during sequencing

Gene	Variant Allele Frequency (%)
NF2	39.8%
TP53	40.5%
CSMD3	Not provided
RAD50	Not provided
ZFHX3	Not provided
KMT2C	Not provided

CADD Scores – “CADD” is an algorithm that Calculates Combined Annotation Dependent Depletion (CADD)

- Scientists developed *in-silico* prediction tools to assist in assessing the pathogenicity of mutations.
- Multiple *in-silico* prediction tools are available for this purpose (such as PolyPhen, SIFT, GERP *etc.*) …
- Kircher (2014) developed the CADD tool to integrate the information from many functional annotation tools into a single results for ease of use. Also see Schubach 2024
- CADD is a recommended strategy for identification of deleterious/pathogenic mutations according to the guidelines of the American College of Medical Genetics and Genomics (ACMG) and the Association of Molecular Pathology (AMP) [Richards *et al.,* 2015; Pastorino *et al*., 2018].

Gene	CADD Score ≥ 20
NF2	37
TP53	26.1
CSMD3	23.8
RAD50	26
ZFHX3	N/A
KMT2C	15.18

VAF %s and CADD Scores – Objective, Reproducible, Quantitative, Peer Reviewed Data Regarding Mutations

Gene	Variant Allele Frequency (%)	Variant Interpretation	Mutation/DNA Alteration	Protein Alteration	CADD Score ≥ 20
NF2	39.8%	Pathogenic*	c.1261G>T	p.E421*	37
TP53	40.5%	Likely Pathogenic*	c.716A>G	p.N239S	26.1
CSMD3	Not provided	VUS	c.7441C>A	p.L2481I	23.8
RAD50	Not provided	VUS*	c.2702T>C	p.L901S	26
ZFHX3	Not provided	VUS	c.2322_2348del27	p.A776_A784del	N/A
KMT2C	Not provided	VUS	c.4807G>A	p.A1603T	15.18

Notable Rulings on Defense Motions to Compel Genetic Testing

Case	Plaintiff's National Counsel	Comments
Valadez – CA 2023	Kazan McClain	Plaintiff win - in this case heavily focused on cosmetic talc, the now departed Alameda asbestos Judge Seabolt (erroneously) denied any use of genetics in this pericardial mesothelioma case, citing timing, procedural and substantive factors; case resolved after trial that showed extensive family cancer history, including the death of plaintiff's father at 38 because of a rare bone cancer and plaintiff developed pericardial meso by 22
Sotomayor – CA - 2024	Kazan McClain	Defense win - Judge Seigle – Los Angeles - allowed BAP1 testing, citing Dr. Testa's 2022 genomic causation admission in Watts deposition and relevance of genetics to plaintiff's prognosis/survival
McCabe – HI 2023	Waters Kraus	Defense win - motion granted; order did not limit scope of sequencing, but parties disagreed on scope; sequencing results barred because of late arrival; plaintiff claimed a genetics expert was needed and refused to rely solely on Dr. Kradin for genetics
Beckwith – WA 2023	Maune Raichle	Defense win - order did not limit scope of sequencing; case resolved soon after order entered
Gonzalez – MA 2023	Thornton	Defense win - order rejected premature ruling on the merits of genomic defense and approved sequencing of 14 genes

Never Correct, Obsolete Cowger Ruling on Defense Motion to Compel Whole Genome Sequencing

Case	Plaintiff's National Counsel	Comments
Cowger – Chicago 2020	Cooney & Conway Weitz & Luxenberg	Plaintiff agreed to BAP1 testing, but defense sought whole genome sequencing, which was denied by Judge McWilliams The Cowger order was never correct under the Frye standard because Judge McWilliams relied on Dr. Testa's personal opinions instead of statements set out in numerous peer reviewed studies Dr. Testa testified that whole genome sequencing was "not even done for research" and would be "beyond the pale," but 6 months later he published the results of whole genome sequencing of 14 people with mesothelioma See Order at 5 (quoting Dr. Testa's testimony that "sequencing of a person's whole genome "hasn't even been done in research, [as it would go] way beyond the pale."" (See Exhibit A, at p. 3 (citing T. 74) (quoting T. 187) (emphasis omitted)).

Notable Ongoing Defense Motions to Compel Genetic Testing

Case	Plaintiff's National Counsel	Comments
Mizer – NJ	Maune Raichle	Judge Viscomi has allowed "all hands" briefing and has said she anticipates an evidentiary hearing Judge Viscomi also sent a letter to counsel outlining topics to consider addressing – see link for letter https://www.dropbox.com/scl/fi/ykrz0irz5glpciicshurs/Judge-Viscomi-letter-re-2024-5.15.24-Genetic-Testing-for-Mesothelioma-1-1.pdf?rlkey=5spjq2cfvxurwxz301eqcuc3g&dl=0
Craft – LA	Barron & Budd	Motion for whole genome sequencing in lung cancer case; tumor testing already established presence of *EFGR* mutation with a VAF percentage in the 30-70% range that identifies likely germline mutations

Notable Differential Etiology Rulings When Plaintiff Blocked Access to Genetic Testing Data

Case	Plaintiff's National Counsel	Comments
Prudencio – CA 2021	Kazan McClain	In a cosmetic talc trial, Judge Kaus in Alameda allowed the defense to introduce evidence of genetic testing that the doctor ordered but the testing was never done
McCabe – HI 2023	Waters Kraus	Trial judge allowed cross-examination of Dr. Kradin regarding the absence of genetic testing data (the judge had barred the sequencing data as arriving too late)
Sotomayor – CA - 2024	Kazan McClain	Plaintiff moved in limine to bar tumor testing data after trial judge denied most defense requests for germline testing; case resolved prior to a ruling

Notable California Evidence Code Change

Case	Plaintiff's National Counsel	Comments
Change to California evidence code		Plaintiff's bar obtained a revision to Cal. Ev. Code 801.1. The new code requires that for an opposing expert to offer testimony contrary to the medical causation testimony of the expert for the party bearing the burden of proof, the expert must be able to opine that the alternative cause exists to a reasonable medical probability, *except* as provided in subdivision (b). • Multiple articles on the code change. E.g. California Evidence Code 801.1: What You Need To Know About the New California Law Governing Expert Testimony https://www.arnoldporter.com/en/perspectives/advisories/2023/12/california-evidence-code-801-1

Missing Genetic Data – “Family Matters” article

- “Many patients with mesothelioma are involved with litigation when it comes to their personal diagnosis of mesothelioma due to exposure to asbestos.”
- “Many of these patients are rightfully concerned that if a germline mutation is identified, this can be used against them. That is, the defense could argue that the asbestos exposure had little to no effect on cancer diagnosis and that the cause of the cancer was due to an underlying predisposition to mesothelioma….”
- “It is imperative that genetic counselors discuss this potential with patients so that they can make the best decision for themselves regarding genetic testing. Viable alternative options may (1) include a decline in germline genetic testing or (2) choose to undergo genetic testing under a research study to keep this information separate from their medical record.” (emphasis added)”

- The first author is a genetic counselor, F. Hathaway, from the University of Chicago.

  - May 2023 - Hathaway F, Martins R, Sorscher S, Bzura A, Dudbridge F, Fennell DA. Family Matters: Germline Testing in Thoracic Cancers. *Am Soc Clin Oncol Educ Book*. 2023;43:e389956.

  - Open access at https://ascopubs.org/doi/10.1200/EDBK_389956?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

More on Missing Genetic Data - Follow Up “Family Matters” Talk at ASCO 2023

- The following text is from the ASCO-provided transcript of Q & A after the 2023 ASCO Family Matters panel presentation by Ms. Hathaway, Dr. Fennell and others:

“•SPEAKER [3 Dr. Fennell]: …What do you do if you have experience of germline mutation in a particular patient affecting the likelihood of successful litigation?”

“•SPEAKER [1 Ms. Hathaway]: Yeah, so, so far, they haven't been able to have access to the testing itself. So interesting enough, at least in the United States, this is why Dr. Kindler set up her research, mainly to avoid having to disclose that when they ask for health records.”

- “…which is why I would say that the majority of my mesothelioma patients that we see when they come back positive under the research study, I've yet to have anybody want to do clinical-based testing after getting--knowing that they have their mutation research-wise, because we don't put it in the medical record at that point.”

- “We do talk to the patient's family members. We encourage them to call us and tell--and go over what does this mean.”

- Video and transcript are available to ASCO members at the following link:https://meetings.asco.org/2023-asco-annual-meeting/15123?presentation=215121#215121

2023 Amendments to FRE 702

Pre-amendment

- A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:
- *[(a) through (c) unchanged]*
- (d) the expert has reliably applied the principles and methods to the facts of the case.

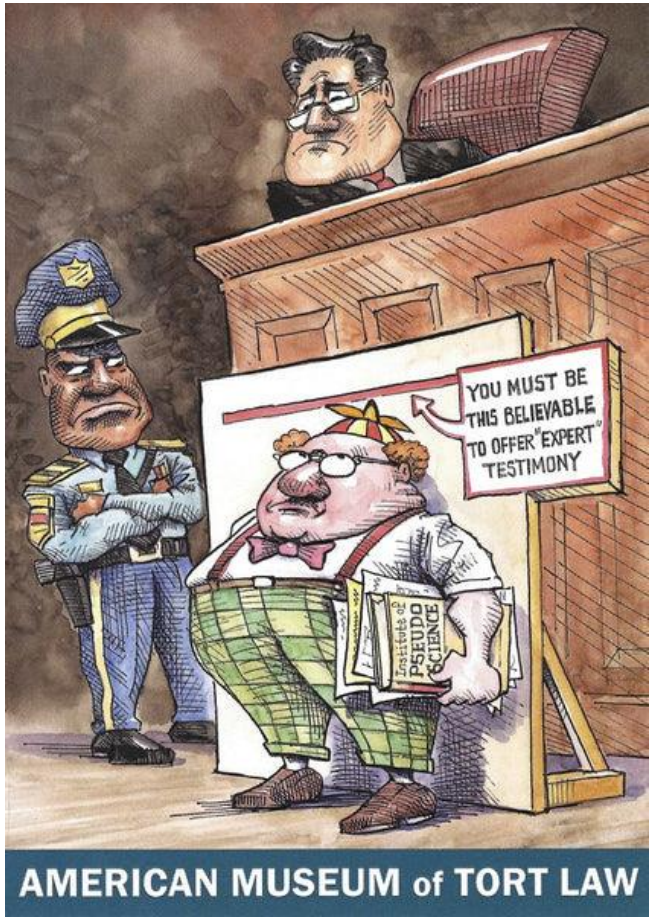
As amended

- [same, with the addition of] ***the proponent demonstrates to the court that it is more likely than not that***:
- *[(a) through (c) unchanged]*
- (d) the expert's opinion reflects a reliable application of the principles and methods to the facts of the case.

2023 Amendments to FRE 702: Advisory Committee Notes

- "… the rule has been amended to clarify and emphasize that expert testimony may not be admitted unless the proponent demonstrates to the court that it is **more likely than not that the proffered testimony meets the admissibility requirements** set forth in the rule."

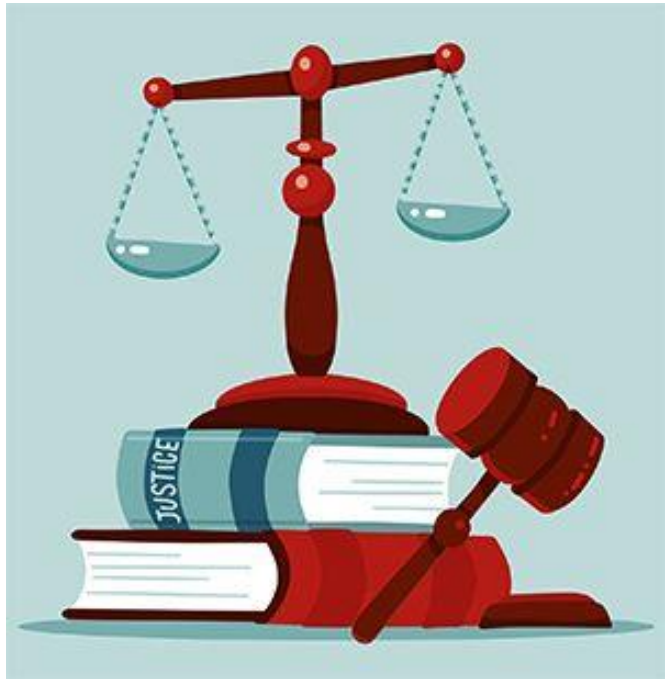
OMG! DID EVERYTHING CHANGE?!?!?!



2023 Amendments to FRE 702: Advisory Committee Notes (cont'd)

- **Advisory Committee Notes, 2000 Amendments:**

  - "… the admissibility of all expert testimony is governed by the principles of Rule 104(a). Under that Rule, ***the proponent has the burden of establishing that the pertinent admissibility requirements are met by a preponderance of the evidence***."



2023 Amendments to FRE 702

(cont'd)

What's that?

- Advisory Committee Notes, 2023 Amendments:

"The amendment ***clarifies that the preponderance standard applies*** to the three reliability-based requirements added in 2000 …."

- "The intent of the rule change is to focus and direct district courts to conduct the gate-keeping inquiry enunciated in *Daubert* and refrain from bypassing the admissibility determination in favor of a question of weight to be decided by a fact finder." ***Vasquez v. Johnson*, C.A. 22-150-SDD-RLB, 2024 WL 2194871 (M.D. La., Feb. 7, 2024).**

- "The amended Rule now requires courts to determine that "it is more likely than not" that the four factors are satisfied before allowing an expert witness to testify." ***Perrone v. Catamount Ski Resort, LLC*, No. 1:20-CV-563 (AMN/CFH), 2024 WL 2078664 (N.D.N.Y. May 9, 2024).**

2023 Amendments to FRE 702

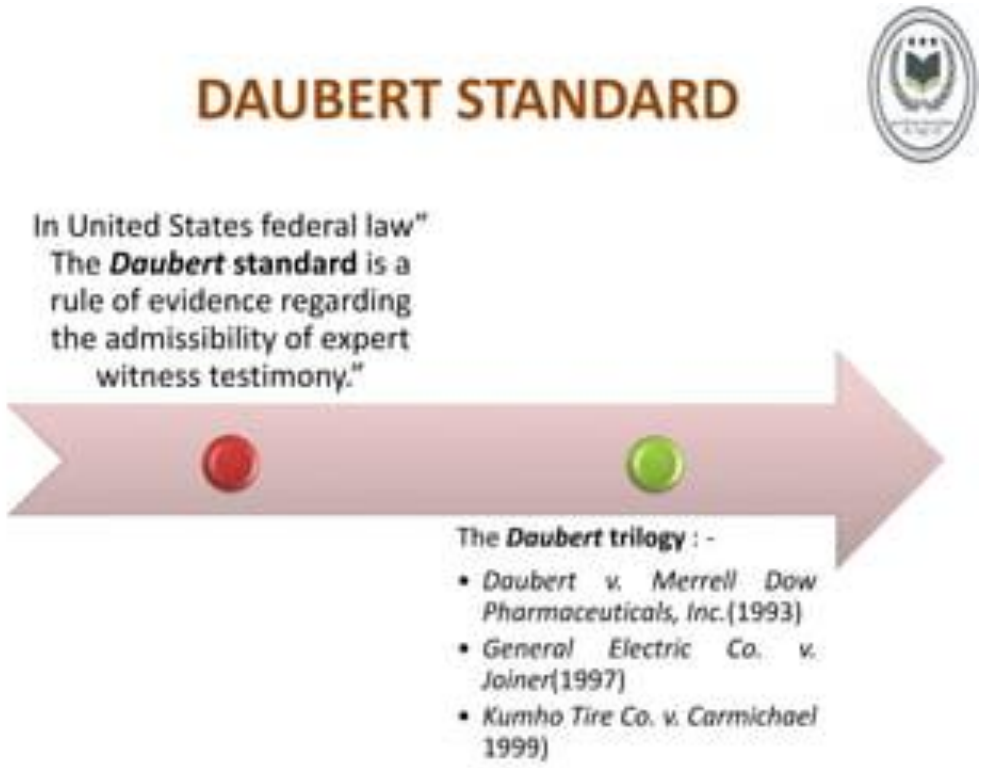
(cont'd)

- 2023 amendments to FRE 702 **CLARIFIED** the trial court's gatekeeping function with respect to expert opinion testimony, but **DID NOT CHANGE** standards or procedures for performing the gatekeeping function.

- **Advisory Committee Notes, 2023 Amendments:**

"***Nothing in the amendment imposes any new, specific procedures***. Rather, the amendment is ***simply intended to clarify*** that Rule 104(a)'s requirement applies to expert opinions under Rule 702."

But what about *Daubert* in the Talc MDL?



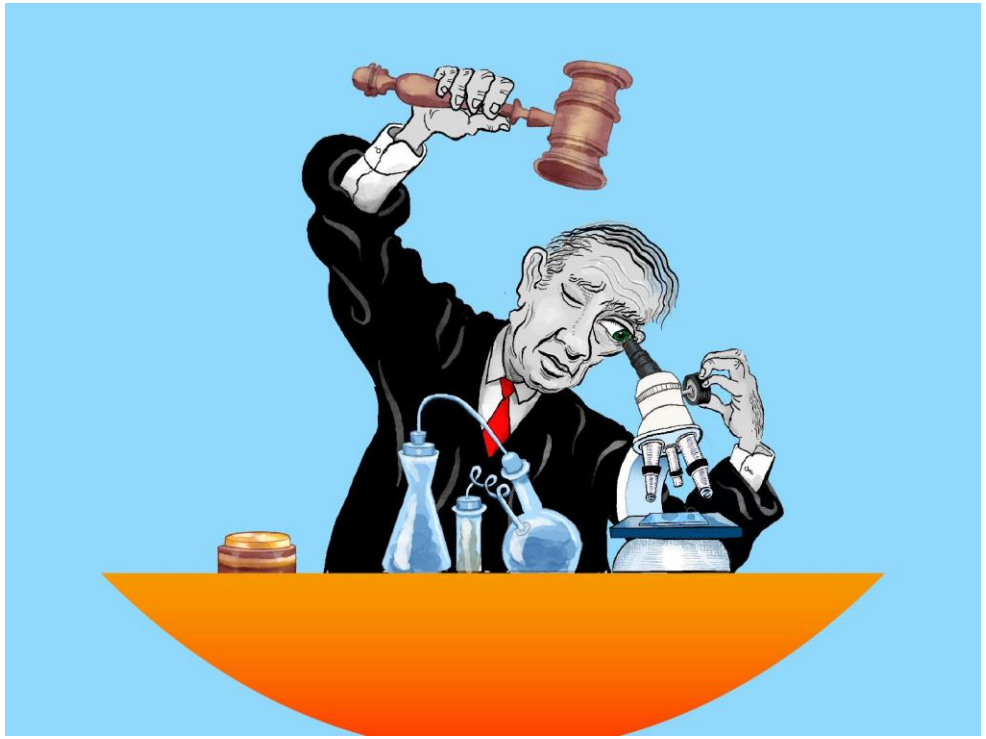
- **Talc MDL, Judge Shipp's March 27, 2024 Text Order re: *Daubert*:**

"… recent changes to [FRE 702] the emergence of new relevant science, and the language of Chief Judge Wolfson's previous *Daubert* Opinion make a **full refiling of *Daubert* motions** appropriate."

But what about *Daubert* in the Talc MDL?

(cont'd)

- PSC moved to reconsider Judge Shipp's order reopening *Daubert* as to issues decided by Judge Wolfson in 2020.



- **Talc MDL, Judge Shipp's April 30, 2024 Order re: *Daubert*:**
  - Motion denied.

1) Judge Wolfson contemplated that her *Daubert* rulings may be subject to change as new scientific knowledge propagated over time.

2) Defendants provided at least some evidence that medical science changed over the last three years.

1) "… Defendants should be allowed to contest previous *Daubert* holdings by this Court should Defendants be able to identify any incorrect application of Rule 702 in the 2020 Opinion."

   - Judge Shipp agreed that the amendments to FRE 702 "did not change evidentiary standards, but clarified them."

But what about *Daubert* in the Talc MDL?

(cont'd)

- **Talc MDL, Judge Shipp's April 30, 2024 Order re: *Daubert***:

- "… if Chief Judge Wolfson entered a decision on an issue and either party wishes to challenge that decision, … the briefing should identify **either**:

  1) that Chief Judge Wolfson's previous Opinion demonstrably fails to adhere to Rule 702 as clarified by the 2023 amendments; **or**

  2) new science is shown to directly contradict or challenge Chief Judge Wolfson's previous findings.

But what about *Daubert* in the Talc MDL?

(cont'd)

New Stuff?

Intimate Care Products and Incidence of Hormone-Related Cancers: A Quantitative Bias Analysis

Katie M. O'Brien, PhD, MSPH[1]; Nicolas Wentzensen, MD, PhD, MS[2]; Kemi Ogunsina, MD, PhD, MPH[1]; Clarice R. Weinberg, PhD[3]; Aimee A. D'Aloisio, PhD, MS[4]; Jessie K. Edwards, PhD, MSPH[5]; and Dale P. Sandler, PhD[1]

DOI https://doi.org/10.1200/JCO.23.02037

CONCLUSION Although results show how differential recall would upwardly bias estimates, corrected results support a positive association between use of intimate care products, including genital talc, and ovarian cancer.

https://pubmed.ncbi.nlm.nih.gov/38748950/

New Jersey 104 *Daubert* Hearings

- Judge Viscomi's invitation for "all hands" briefing regarding pre-disposition to mesothelioma, in anticipation of a 104 hearing.

- Judge Viscomi scheduled 104 hearings for multiple plaintiffs' experts and defendants' experts over the course of 15 days through July 2024.
  - On May 22, 2024, Judge Viscomi notified interested parties stating, "[i]t is the intent of the court to not permit new 104 hearings as to these experts on the same issue without a showing as to necessity pursuant to Accutane and progeny, e.g., a new testing methodology would require a new 104 hearing as to that issue."

FDA Testing

Years	Product Types	Testing Methods	Number of Products/ Samples	Number of Samples Positive for Asbestos
2009-2010	Raw talc, makeup, body powder	PLM+TEM	61	0
2019	Makeup, body powder	PLM+TEM	52	9
2021	Makeup, body powder	PLM+TEM	50	0
2022	Makeup, body powder	PLM+TEM	50	0
2023	Hair color, hair powder, makeup	PLM+TEM	53	0

Source: FDA, 2024

Modernization of Cosmetics Regulations Act of 2022 (MoCRA)

- Updates Federal Food, Drug, and Cosmetic (FD&C) Act of 1938
- Facility and product registration
- Reporting of adverse health events
- Authority to require a mandatory recall of cosmetics
- Labeling requirements
- Manufacturers must adhere to current Good Manufacturing Practices (cGMPs)
- **Will require testing for talc**

FDA Talc Testing Method Timeline

- **2018:** FDA establishes the Interagency Working Group on Asbestos in Consumer Products (IWGACP).
- **2019:** FDA testing of various cosmetic talc products detects asbestos.

FDA STATEMENT

Statement from FDA Commissioner Scott Gottlieb, M.D., and Susan Mayne, Ph.D., director of the Center for Food Safety and Applied Nutrition, on tests confirming a 2017 finding of asbestos contamination in certain cosmetic products and new steps that FDA is pursuing to improve cosmetics safety

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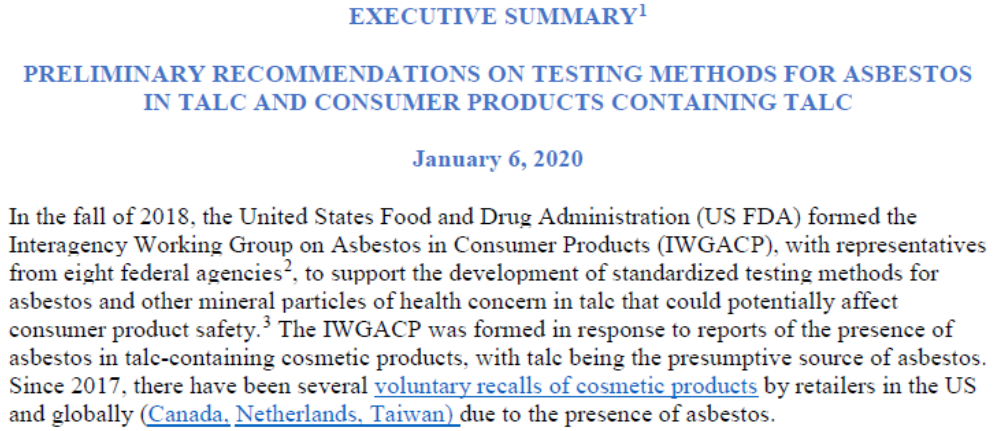
For Immediate Release: March 05, 2019

https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-susan-mayne-phd-director-center-food-safety-and

FDA Talc Testing Method Timeline (cont'd)

- **January 2020:** IWGACP issues Executive Summary with preliminary recommendations for testing methods.



EXECUTIVE SUMMARY[1]

PRELIMINARY RECOMMENDATIONS ON TESTING METHODS FOR ASBESTOS IN TALC AND CONSUMER PRODUCTS CONTAINING TALC

January 6, 2020

In the fall of 2018, the United States Food and Drug Administration (US FDA) formed the Interagency Working Group on Asbestos in Consumer Products (IWGACP), with representatives from eight federal agencies[2], to support the development of standardized testing methods for asbestos and other mineral particles of health concern in talc that could potentially affect consumer product safety.[3] The IWGACP was formed in response to reports of the presence of asbestos in talc-containing cosmetic products, with talc being the presumptive source of asbestos. Since 2017, there have been several voluntary recalls of cosmetic products by retailers in the US and globally (Canada, Netherlands, Taiwan) due to the presence of asbestos.

https://www.fda.gov/media/134005/download

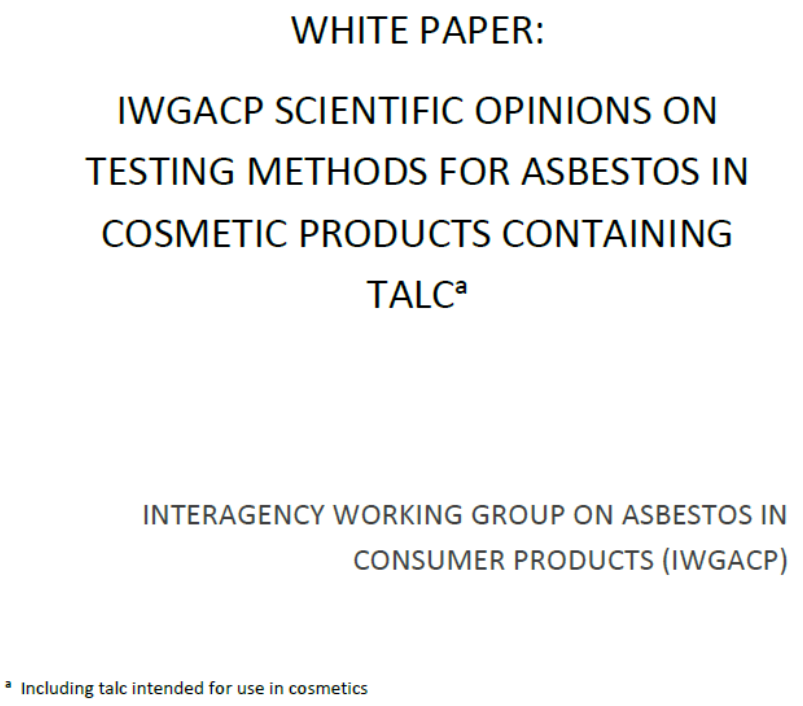
- **February 4, 2020:** FDA holds public meeting entitled "Testing Methods for Asbestos in Talc and Cosmetic Products Containing Talc."

https://www.fda.gov/cosmetics/cosmetics-news-events/public-meeting-testing-methods-asbestos-talc-and-cosmetic-products-containing-talc-02042020

FDA Talc Testing Method Timeline (cont'd)

- **March 2020:** [Pause for pandemic ….]

- **December 2021:** IWGACP issues the White Paper "to inform FDA's consideration of testing methods for talc-containing cosmetics and talc intended for use in cosmetics."



WHITE PAPER:

IWGACP SCIENTIFIC OPINIONS ON TESTING METHODS FOR ASBESTOS IN COSMETIC PRODUCTS CONTAINING TALC[a]

INTERAGENCY WORKING GROUP ON ASBESTOS IN CONSUMER PRODUCTS (IWGACP)

[a] Including talc intended for use in cosmetics

December 2021

FDA Talc Testing Method Timeline (cont'd)

- **December 29, 2022:** Modernization of Cosmetics Regulation Act (MoCRA) of 2022 becomes law.

Why?

uncertainty, complexity and risks. And at the same time, the provisions in the Federal Food, Drug, and Cosmetic Act (FD&C Act) – the law governing the FDA's oversight of cosmetic products — have not been updated since it was first enacted in 1938. The current

FDA STATEMENT

Statement from FDA Commissioner Scott Gottlieb, M.D., and Susan Mayne, Ph.D., director of the Center for Food Safety and Applied Nutrition, on tests confirming a 2017 finding of asbestos contamination in certain cosmetic products and new steps that FDA is pursuing to improve cosmetics safety

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For Immediate Release: March 05, 2019

FDA Talc Testing Method Timeline (cont'd)

- What did MoCRA have to say about talc testing?

SEC. 3505. TALC-CONTAINING COSMETICS.

The Secretary of Health and Human Services—

(1) not later than one year after the date of enactment of this Act, shall promulgate proposed regulations to establish and require standardized testing methods for detecting and identifying asbestos in talc-containing cosmetic products; and

(2) not later than 180 days after the date on which the public comment period on the proposed regulations closes, shall issue such final regulations.

December 29, 2022 (date of enactment) + 1 year = **December 29, 2023**

AND THE PROPOSED METHOD IS ….

FDA Talc Testing Method Timeline (cont'd)

…. Not here yet. ***BUT***:

FDA Releases Data from the Agency's 2023 Testing of Talc-Containing Cosmetic Products for Asbestos

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Cosmetics Constituent Update

April 5, 2024

To see FDA's previous talc sampling results, please visit FDA's webpage on Talc. As required under the Modernization of Cosmetics Regulations Act of 2022 (MoCRA), FDA intends to promulgate proposed regulations to establish and require standardized testing methods for detecting and identifying asbestos in talc-containing cosmetic products.

https://www.fda.gov/cosmetics/cosmetics-news-events/fda-releases-data-agencys-2023-testing-talc-containing-cosmetic-products-asbestos

Meanwhile,

A long time ago in a galaxy far, far away….

Modernization of Asbestos Testing in USP Talc

- **April 2010:** USP announces a monograph modernization initiative.

- **November 16, 2010:** FDA tells USP to update the USP Talc Monograph:

DEPARTMENT OF HEALTH & HUMAN SERVICES

COPY

NOV 16 2010

Attached is a list of drug and excipient monographs that, for the reasons cited in the spreadsheet, we have determined to be most in need of modernization. Additional articles may follow. We hope you will find this useful in your revision efforts.

Attachment: List and Rationale of Drug and Excipient Monographs Most in Need of Modernization

Monograph(s)	Rationale
Talc	Labeling should be revised to match the statements that are provided in the Talc FCC monograph, thereby assuring that Talc is not sourced from mines that are known to contain asbestos. Also, USP should consider revising the current tests for asbestos to ensure adequate specificity.

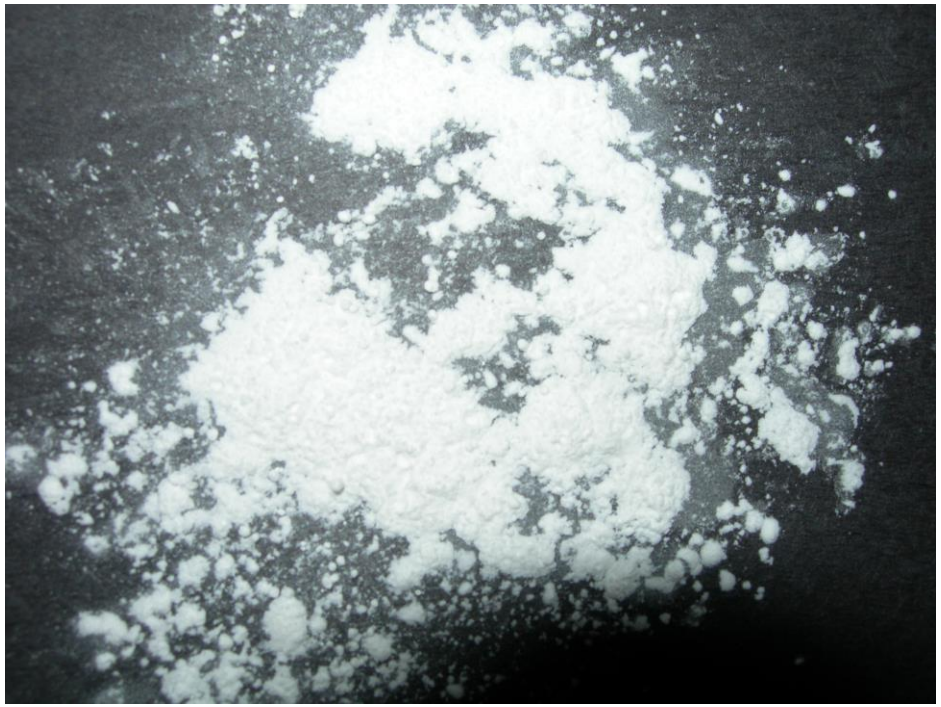
But What Is the USP Talc Monograph?

- "The USP Talc monograph contains requirements applicable to talc for pharmaceutical applications."

  https://www.usp.org/frequently-asked-questions/talc-monograph

"Absence of Asbestos" Requirement:

- First, sample analyzed by either **infrared absorption (IR)** or **x-ray diffraction (XRD).**
- Second, if asbestos is detected by either IR or XRD, sample analyzed by polarized light microscopy.



Modernization of Asbestos Testing in USP Talc

(cont'd)

- **December 20, 2010:** USP responds to FDA's request to modernize the USP Talc Monograph.

U.S. Pharmacopeia
The Standard of Quality℠

December 20, 2010

Larry Ouderkirk
Co-Chair, Monograph Modernization
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, Maryland

Paul Seo, Ph.D.
Co-Chair, Monograph Modernization Task Group
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, Maryland

Re: Letter dated November 16, 2010

4. Talc

Although Talc is a PDG harmonized monograph, USP will add the labeling requirements for absence of talc currently included in the FCC monograph as a non-harmonized attribute. USP also will eliminate the current two "screening" methods of IR and XRD that are part of the Absence of Asbestos test and retain the optical microscopy test as the *single* test method.

Modernization of Asbestos Testing in USP Talc

(cont'd)

- **May 2011:** Rather than immediately eliminating IR and XRD, USP creates talc **"expert panel"** to evaluate alternative methods for determining the absence of asbestos.

Modernization of Asbestos Testing in USP Talc

(cont'd)

2014 Stimuli to the Revision Process

- Conclusions of the USP EP Panel:
  - "The USP Talc Expert Panel's recommendation for revision of the test for *Absence of Asbestos* will include **omission of the IR spectroscopy test** and **inclusion of a revised XRD procedure in combination with one or more microscopic evaluations (PLM, TEM, or SEM)**."
  - "**The panel also recommends including additional sample preparation/concentration methods** to improve the feasible limits of detection as indicated."

Modernization of Asbestos Testing in USP Talc

(cont'd)

What's next?

General Chapter Prospectus: <901> Detection of Asbestos in Pharmaceutical Talc

Posting Date: 30-Apr-2021; updated 09–Aug–2021*
Expert Committee: Excipients Test Methods
Input Deadline: 30-May-2021

Proposed New Title: <901> *Detection of Asbestos in Pharmaceutical Talc*

Background and objective: In response to a request from FDA's Monograph Modernization Task Group in 2010 to revise the asbestos test in the *USP* Talc monograph, USP intends to develop a new general chapter which can be cross-referenced by the Talc monograph revision for detection of asbestos in pharmaceutical Talc.

Preliminary outline: The following represents the sections for the proposed General Chapter:

- INTRODUCTION
- X-RAY DIFFRACTION (XRD) – also termed X-Ray Powder Diffraction (XRPD). It can be used for determining overall purity of a talc product with respect to accessory minerals and can be important in determining general suitability for pharmaceutical use. This test method is used to identify and determine a relative level (presence or absence) of total amphibole and total serpentine in a talc powder matrix. It is intended to be used in combination with the PLM microscopy technique. Detailed testing procedure and acceptance criteria for XRD are described in this section.
- POLARIZED LIGHT MICROSCOPY (PLM) - PLM is used to identify asbestos particles in a talc powder matrix. It is intended to be used with XRD as a complimentary microscopy technique. It can detect asbestos at a lower level than XRD and it can differentiate different types of asbestos. Detailed testing procedure and acceptance criteria for PLM are described in this section.

https://www.uspnf.com/notices/gc-901-prospectus-20210430

Modernization of Asbestos Testing in USP Talc

(cont'd)

So, when?

Talc, <901> Detection of Asbestos in Pharmaceutical Talc, <1901> Theory and Practice of Asbestos Detection in Pharmaceutical Talc

Type of Posting: General Announcement
Posting Date: 26-May-2023
Expert Committees: Simple Excipients, Excipients Test Methods

The X-ray diffraction (XRD) and polarized light microscopy (PLM) testing methods in the *PF* 48(2) proposals are not routine analyses in quality control labs, and, as such, the revisions to the *USP* Talc monograph may require additional time for industry to adopt and prepare for compliance. Therefore, the SE EC approved an extended official date of December 1, 2025, with changes anticipated to be published in *USP–NF* 2023, Issue 3. The extended official date is intended to provide the time needed by manufacturers and users to implement the test methods and make necessary changes.

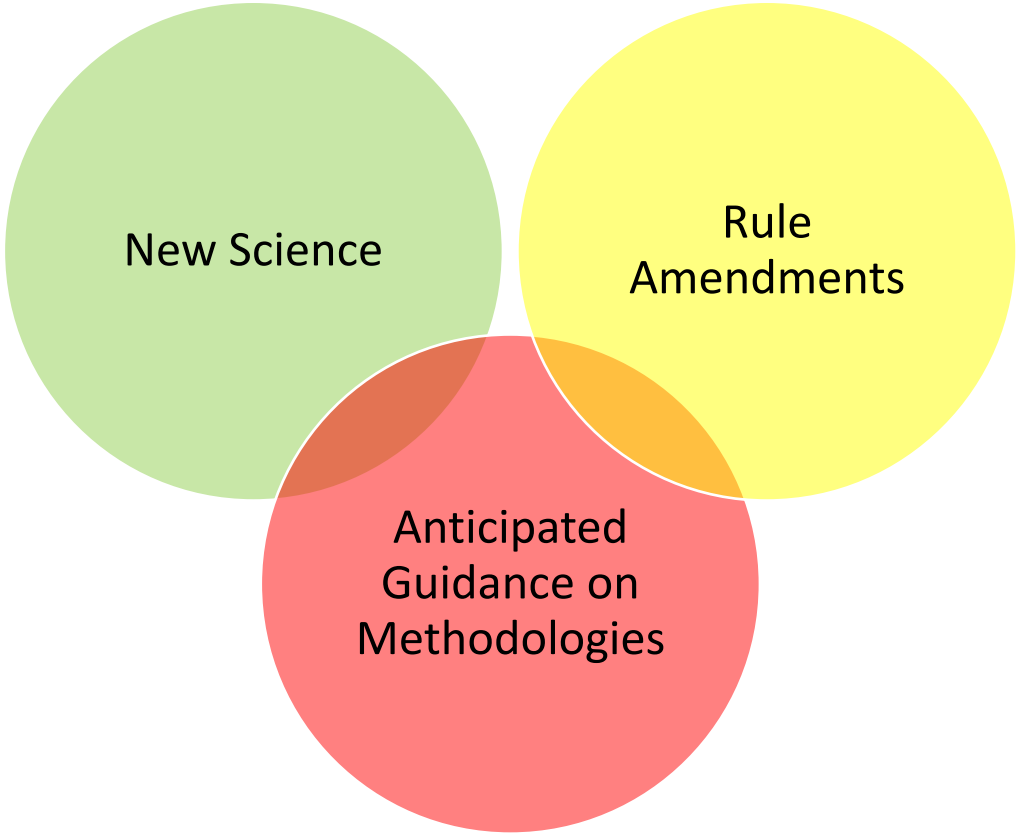
In summary, below are the respective anticipated official dates for the USP Talc monograph and general chapters <901> and <1901>:

1. The USP Talc monograph revision is anticipated to be published in *USP-NF* 2023, Issue 3 and become official on **December 1, 2025**.
2. General chapters, <901> and <1901>, are anticipated to be published *USP-NF* 2023, Issue 3 and become official on **December 1, 2023**.

https://www.uspnf.com/notices/talc-official-dates-20230601

Going Back to the Beginning…

How do litigants and courts navigate new science, amendments to rules, and anticipated guidance on methodologies?



THANK YOU

Emily Goswami, MS, CIH, Technical Director, Roux, Oakland, CA
Kirk Hartley, Esq., LSP Group, Chicago, IL
Mark A. Linder, Esq., The Lanier Law Firm, Houston, TX
Karlene Manley, Esq., CMBG3 Law, Boston, MA

Reference List

- Ciocan, C., Pira, E., Coggiola, M., Franco, N., Godono, A., La Vecchia, C., ... & Boffetta, P. (2022). Mortality in the cohort of talc miners and millers from Val Chisone, Northern Italy: 74 years of follow-up. Environmental Research, 203, 111865.
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