

THE STATE OF SOUTH CAROLINA
In The Court of Appeals

APPEAL FROM RICHLAND COUNTY
Court of Common Pleas
Jean H. Toal, Circuit Court Judge

Appellate Case No. 2025-000065
Civil Action No. 2023-CP-40-04072

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SC Court of Appeals

Michael L. Perry and Lonnie Long,.....

Respondents,

v.

American International Industries et al.

Of whom Johnson & Johnson; LLT Management, LLC
f/k/a LTL Management, LLC; Kenvue, Inc.; and Johnson
& Johnson Holdco (NA), Inc. are the

Appellants.

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I certify that this Designation does not contain any matters which are irrelevant to this appeal.

JNJ000578955

Metadata

AttachCount	0	ORIGINAL
BegAttach	JNJ 000578954	ORIGINAL
Confidentiality	N	ORIGINAL
Custodian	Legacy 2	ORIGINAL
DateMod	09/23/1974 12:00 AM	ORIGINAL
EndAttach	JNJ 000578955	ORIGINAL
FileName	J&J0123239.TIF	ORIGINAL
FileSize	0.00	ORIGINAL

STATE OF SOUTH CAROLINA	)	IN THE COURT OF COMMON PLEAS
	)	
COUNTY OF RICHLAND	)	FOR THE FIFTH JUDICIAL CIRCUIT
	)	
MICHAEL L. PERRY and	)	C/A NO. 2023-CP-40-04072
LONNIE L. LONG,	)	
	)	<i>In Re:</i>
Plaintiffs,	)	Asbestos Personal Injury Litigation
	)	Coordinated Docket
v.	)	
	)	
AMERICAN INTERNATIONAL	)	
INDUSTRIES, et al.	)	
	)	
Defendants.	)	

**PLAINTIFFS' MOTION IN LIMINE NO. 17 TO EXCLUDE
THE TESTIMONY OF DR. GREGORY DIETTE**

Pursuant to Rules 702 and 403 of the South Carolina Rules of Evidence, Plaintiffs hereby move to exclude the testimony of Dr. Gregory Diette because his opinions regarding alleged spontaneous mesotheliomas lack an adequate foundation and admission of this testimony would confuse and mislead the jury.

INTRODUCTION

Dr. Diette is a pulmonologists offered as an expert by Defendants. He is offered by Defendants Avon Products, Inc., and Johnson & Johnson ("J&J"). Dr. Diette is also offered by Defendants PTI Union (for Gold Bond and Ammens), The Estee Lauder Companies, IMI Fabi, and Vi-Jon (for Equate). Although Dr. Diette holds a joint position at the Johns Hopkins School of Public Health, the primary focus of his research and work is pulmonary diseases such as chronic obstructive pulmonary disease and asthma. He does not specialize in any way in either mesothelioma or even cancer generally.

Plaintiffs ask that Dr. Diette's opinions concerning Plaintiff Michael Perry's mesothelioma be excluded.¹ His opinions on this topic are based on an inadequate foundation, are speculative at best, and will be misleading and confusing to the jury. Plaintiffs seek to exclude the following opinions offered by Dr. Diette: (1) that Mr. Perry's mesothelioma was spontaneous or naturally occurring; (2) that Mr. Perry's mesothelioma occurred because of genetic mutations; and (3) that the talcum powder at issue in these cases did not contain asbestos and/or did not elevate Mr. Perry's risk of developing mesothelioma.

Plaintiffs made this same motion against Dr. Diette in the *Payne* and *Plant* cases, which was granted in part. There, this Court limited Dr. Diette's testimony in that he was not permitted to give a specific causation opinion that the plaintiff's mesothelioma was "spontaneous":

I am going to partially grant and partially deny the plaintiff's motion in limines with respect to Dr. Gregory Diette, Dr. David Weill, and Dr. Allan Feingold.

And the limitation is going to be this: I am going to -- I wrote it down. I am going to rule that those witnesses may testify generally about cosmetic talc and about asbestos and cosmetic talc and about how that affects the contraction of mesothelioma.

They will not be allowed to opine about the cause of the mesothelioma that has been contracted by Sarah Plant or by Shelby Linville Payne. So they can be a part of the expert testimony about this subject. Of course, as time moves on and they begin to testify, I may have some rulings that will still be required to be made as the trial moves forward. But I am not going to forbid them from testifying as requested. But I am going to limit their testimony, and I pray that my limitation will be obeyed by them, as it was not by Dr. Attanoos.

Because that's the way I would like it to be is they can testify as experts. Of course, they will be subject to some rather severe cross-examination. As we know, that's all part of what takes place.

But they will not be able to testify specifically about the cause of mesothelioma in Plant and Payne.²

The same limitation is warranted here. As in the *Payne* and *Plant* matters, Dr. Diette offers (or will offer) opinions about spontaneous mesothelioma without any scientific foundation.

¹ Ex. 1, Diette Report, 6/27/24; Ex. 2, Diette Supplemental Report, 7/2/24.

² Ex. 19, *Payne/Plant* MIL Hearing Tr., 2/15/23, at 196:15-197:22.

Spontaneous mesothelioma is not a cause, it is a speculative statement that Dr. Diette does not know the cause. This is not proper expert testimony, it will not assist the jury, and it should be excluded.

STANDARD OF REVIEW

Rule 702 of the South Carolina Rules of Evidence provides that “[i]f scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise.” The trial court must act as a gatekeeper over scientific evidence and make three preliminary findings before expert testimony may be admitted. *Watson v. Ford Motor Co.*, 389 S.C. 434, 446, 699 S.E.2d 169, 175 (2010). The Court must find “that expert testimony is necessary to assist the jury in resolving factual questions, the expert is qualified in the particular area, and the testimony is reliable.” *Id.* at 446-47, 699 S.E.2d at 175. “In South Carolina, a trial court minding the Rule 702 gate must assess not only (1) whether the expert’s *method* is reliable (i.e., valid), but also (2) whether the *substance* of the expert’s testimony is reliable.” *State v. Warner*, 430 S.C. 76, 86, 842 S.E.2d 361, 365–66 (Ct. App. 2020), *aff’d in part and remanded*, 436 S.C. 395, 872 S.E.2d 638 (2022). A trial court does not abuse its discretion under Rule 702 by excluding the testimony of medical experts whose conclusions were not supported by the data and experiments upon which they relied. *Id.* (citing *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)). “A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered.” *Id.* (quoting *Joiner*, 522 U.S. at 146).

Courts evaluating the admissibility of scientific expert evidence “must find the evidence will assist the trier of fact, the expert witness is qualified, and the underlying science is reliable.”

State v. Council, 335 S.C. 1, 20, 515 S.E.2d 508 (S.C. 1999). In considering the admissibility of scientific evidence the Court looks at several factors, including: (1) the publications and peer review of the technique; (2) prior application of the method to the type of evidence involved in the case; (3) the quality control procedures used to ensure reliability; and (4) the consistency of the method with recognized scientific laws and procedures. *State v. White*, 382 S.C. 265, 274, 676 S.E.2d 684 (S.C. 2009) (citing *Council*, 335 S.C. at 19).

This type of evidence is also subject to attack for relevancy and prejudice. *Id.* at 19–20, 515 S.E.2d at 517.

ARGUMENTS AND AUTHORITIES

I. Dr. Diette’s opinion that Mr. Perry’s mesothelioma was “spontaneous” or “naturally occurring” should be struck.

Dr. Diette’s primary opinion is that Mr. Perry’s mesothelioma most likely occurred spontaneously, although he could not “rule out a contribution to his mesothelioma from his reported asbestos exposures at work.”³ He clarified in his Supplemental Report that he has “not seen evidence in this case of any significant exogenous exposure (including asbestos) that would raise [Mr. Perry’s] risk of developing pleural mesothelioma”⁴ He continues to maintain that “[i]f Mr. Perry did not have significant exogenous exposure from commercial amphibole asbestos, it is most likely that his mesothelioma developed spontaneously or was naturally occurring.”⁵

Dr. Diette has not reviewed data regarding the asbestos content of the talc products at issue, but simply finds it “not plausible” that the asbestos content of these products could cause Mr. Perry’s mesothelioma.⁶ In the past, Dr. Diette has admitted that there is no scientific literature to

³ **Ex. 1**, Diette Report, at 63.

⁴ **Ex. 2**, Diette Supplemental Report, at 4.

⁵ *Id.*

⁶ **Ex. 1**, Diette Report, at 64.

support the conclusion that a mesothelioma can be caused “spontaneously” when there is a history of asbestos exposure:⁷

A. History and evolution of the “background rate” of mesotheliomas in people not exposed to asbestos in the literature.

Dr. J. Corbett McDonald and Dr. Alison D. McDonald were the first to propose a rate of mesothelioma for people not exposed to asbestos.⁸ They reasoned that children with mesothelioma had insufficient latency for their disease to be caused by asbestos and noted that the best estimate of the incidence of mesothelioma in children under 19 years old is 1 per ten million person-years.⁹ Extrapolating backwards from epidemiological studies to find the point where male and female rates converge, they suggested a rate in non-exposed adults of 1 to 2 per million population. They cautioned, however, that this evidence depends on extrapolation, “an essentially speculative procedure.”¹⁰

Dr. Gunnar Hillerdal was next to explore this issue.¹¹ While he agreed that mesothelioma can occur in the absence of exposure to asbestos, “this background level must be very low – probably much <1 case/million people/year.” *Id.* at 510. Since this figure comes from studies of industrialized countries where background exposure to asbestos is unavoidable, Dr. Hillerdal concluded that, “[w]hat the true figure is can only be guessed.”¹²

⁷ **Ex. 3**, Diette Dep., 2/3/23, at 80:13-21.

⁸ **Ex. 4**, McDonald & McDonald, *Mesothelioma: Is There a Background?*, in *THE MESOTHELIAL CELL AND MESOTHELIOMA* 37 (Jaurand & Bignon, eds., 1994) (“McDonald & McDonald 1994”).

⁹ *See id.* at 41.

¹⁰ *See id.* at 44; *see also Ex. 5*, J.C. McDonald and A.D. McDonald, *The epidemiology of mesothelioma in historical context*, Eur Res J 9:1932-1942 (1996) (“McDonald & McDonald 1996”).

¹¹ *See Ex. 6*, Hillerdal, *Mesothelioma: cases associated with non-occupational and low dose exposures*, Occupational Environmental Medicine 56:505-513 (1999) (“Hillerdal 1999”).

¹² *See id.*

Researchers in Great Britain concluded that there was some evidence to suggest that the rate of “spontaneous” mesotheliomas, those that arose with no asbestos exposure, was around 1 per million.¹³

According to a respected pathology textbook from the United States:

The background environmental mesothelioma incidence rate and especially the true spontaneous rate is probably substantially less than one case per million per year, but the true rate can only be guessed, because no significant control adult population without asbestos fibers in lung tissue can be assembled.¹⁴

Using data from the Surveillance, Epidemiology, and End Results (SEER) registry, Dr. Teta was able to estimate the incidence of mesothelioma in a population with little or no potential for occupational asbestos exposure by limiting her analysis to individuals diagnosed at age of 30 years or older and who attained working age after the Occupational Safety and Health Administration (OSHA) asbestos exposure limits took effect.¹⁵ Teta found that:

The annual rate of mesothelioma for males who met these criteria, and were diagnosed at the age of 30 years or above is 1.15 per million (95% CI: 0.90–1.45) (Table 2). For females, the corresponding rate was 0.94 per million (95% CI: 0.71–1.21) (Table 3). The rate for both groups combined was 1.05 per million (95% CI: 0.87–1.24) (data not shown). Therefore, US annual mesothelioma rates for adults under the age 50 years, who would have little or no potential for asbestos exposure, is about 1 per million.¹⁶

Given that approximately 3300 cases of mesothelioma are diagnosed per year in the United States, “upwards of 300 (1 per million) annually may be unrelated to asbestos exposure.”¹⁷ Dr.

¹³ See **Ex. 7**, Wiggins, [British Thoracic Society] *BTS Statement on malignant mesothelioma in the UK, 2007* Thorax 62 (Suppl. II):ii1-ii19, ii1 (2007) (“BTS Statement”); **Ex. 8**, Moore, *Malignant mesothelioma*, Orphanet Journal of Rare Diseases, 3:34 (2008) (idiopathic or spontaneous mesothelioma occur in the absence of any exposure to asbestos, with a rate of around 1 per million).

¹⁴ **Ex. 9**, DAIL AND HAMMAR’S PULMONARY PATHOLOGY 566 (Tomashefski, ed., 3rd ed. 2008).

¹⁵ **Ex. 10**, Teta, *US mesothelioma patterns 1973-2002: indicators of change and insights into background rates*, European Journal of Cancer Prevention 17:525-534 (2008) (“Teta 2008”).

¹⁶ See *id.* at 528.

¹⁷ See *id.* at 534.

Teta's results were consistent with the estimated number of background cases in Great Britain of 1.08 cases per million population.¹⁸

Plaintiff's expert Dr. David Madigan used the SEER data to update Teta's result.¹⁹ He found a maximum background rate of 2.1 per million person years, a level that still included some exposed individuals.²⁰

Defense expert Dr. Suresh Moolgavkar, in a publication cited to by Dr. Diette, estimated that a background rate of 1 per million person-years for peritoneal mesothelioma and between 2 and 3 million person-years for pleura mesothelioma.²¹ In his report for another recent talc case, however, Dr. Moolgavkar references, without citation, an unprecedented background rate for spontaneous mesothelioma of 3 to 4 per million person-years.²² Dr. Diette offers similar opinions in this case and indeed relies on Dr. Moolgavkar's publication.

B. Dr. Diette's opinions regarding spontaneous mesothelioma lack foundation and are entirely speculative.

Trying to estimate the rate of mesothelioma for people who have not been exposed to asbestos is a difficult task because of the ubiquitous presence of asbestos in the ambient air from decades of commercial and industrial use of asbestos products. Nevertheless, estimating a background rate for people with no exposure to asbestos, the so-called rate of "spontaneous" mesothelioma, is important because it is used to compare to incidents of disease in populations of people, such as talc miners and millers, to the expected or background rate. By inflating the

¹⁸ See **Ex. 11**, Tan, *Projection of mesothelioma mortality in Britain using Bayesian methods*, British Journal of Cancer 103:430-436 (2010) ("Tan 2010"); **Ex. 12**, Delgermaa, *global mesothelioma deaths reported to the World Health Organization between 1994 and 2008*, Bulletin of the World Health Organization 89:716-725C (2011) ("Delgermaa") ("the consensus value for the background level of mesothelioma is approximately 1 per million").

¹⁹ See **Ex. 13**, Report of Dr. David Madigan, 2/1/21 ("Madigan Report").

²⁰ See *id.* at 18, ¶ 67.

²¹ See **Ex. 14**, Moolgavkar, *Pleural and peritoneal mesotheliomas in SEER: age effects and temporal trends, 1973-2005*, Cancer Causes Control 20:935-944, 942 (2009).

²² See **Ex. 15**, Moolgavkar Report, *Hirshberg*, at 39.

background rate, a defense expert can conclude that deaths in the exposed populations are not related to exposure to asbestos but are merely background or spontaneous cases.

Dr. Moolgavkar published in peer-reviewed literature that the background rate was 1 per million person-years for peritoneal mesothelioma and 2 to 3 per million person-years for pleural mesothelioma. In his litigation reports, however, Dr. Moolgavkar has offered an opinion based on an assumed background rate of 3 to 4 per million person-years without any citation. This background rate of 3 to 4 per million person-years has no support in the peer-reviewed literature, is contrary to the prevailing opinion in the medical community that the background rate is likely 1 per million person-years, and, at most, 2 to 3 per million person-years.

It is clear that Dr. Diette's opinions regarding Mr. Perry's mesothelioma allegedly being "spontaneous" or "naturally occurring" are completely speculative. He is able to accomplish this opinion by strategically ignoring all evidence, and his method of coming to this opinion is completely unsupported in any recognized scientific community.

Dr. Diette has not reviewed any evidence about the asbestos content of the talcum powder products at issue, states that he has seen no "objective evidence" of Mr. Perry's asbestos exposure, and then summarily declared that his mesothelioma is "spontaneous."²³ This methodology is only supported by a small handful of publications and does not take into account any asbestos exposure, let alone exposure to asbestos-contaminated cosmetic talcum powder. Therefore, his methodology of review is not reliable or consistent with any recognized scientific principles. Allowing this testimony from a pulmonologist that is completely devoid of any scientific foundation is unhelpful to the jury, will confuse and mislead the jury, and should not be admitted.

II. Dr. Diette lacks an adequate foundation for his opinions that Mr. Perry's mesothelioma was "possibly" the result of genetic mutations and his testimony will not assist the jury.

²³ Ex. 1, Diette Report, at 64.

Dr. Diette's second primary opinion is that "[i]t is *possible* that Mr. Perry has a hereditary risk for developing cancer."²⁴ He incorrectly states that "there is no available germline testing to confirm whether or not he has a hereditary risk factor."²⁵ In his Supplemental Report, Dr. Diette reports that "[i]t is *possible* that Mr. Perry had an inherited genetic risk factor for cancer especially given his young age, and personal and family history of malignancies."²⁶ He again claimed that there was no germline testing to confirm that.²⁷

In fact, as noted in Plaintiffs' MIL No. 11, Michael Perry was tested and his medical records show that he does not have the BAP1 mutation. Dr. Diette's testimony regarding a hypothetical genetic abnormality is pure speculation and ignores the testing reported in Mr. Perry's medical records. Further, Mr. Perry has no prior history of cancer, despite Dr. Diette's vague reference to unspecified "personal . . . history of malignancies."²⁸ This is likely due to a rogue medical record that is clearly not about Mr. Perry²⁹:

He has past medical history of insomnia, HLD, chronic back pain, diverticulitis, allergic rhinitis and mild intermittent asthma. Interim blood work is reviewed from 06/15/23. CBC showed WBC 12.0, Hgb 10.7, MCV 78. CMP showed glucose 109, ALP 137, AST 58, ALT 100. Lipid panel showed total cholesterol 127, LDL 83, HDL 34, triglycerides 50. PSA 0.691.

He has history of allergic rhinitis, HLD, anxiety/depression, insomnia, testicular cancer s/p orchiectomy and chemotherapy (1990) and history of low back pain In past year he has made a job switch, now working remotely for a company doing sales and marketing. He is an engineer by trade. Interim blood work is reviewed from 06/12/23. CMP showed glucose 111. Lipid panel showed total cholesterol 181, LDL 106, HDL 48, triglycerides 134.

Speculative testimony about the possibility of a genetic mutation is not helpful to the jury and should not be allowed.

²⁴ *Id.*

²⁵ *Id.*

²⁶ **Ex. 2**, Diette Supplemental Report, at 4 (emphasis added).

²⁷ *Id.*

²⁸ **Ex. 2**, Diette Supplemental Report, at 4.

²⁹ **See Ex. 16**, MUSC Medical Record.

Further, even if Mr. Perry did have germline mutation other than BAP1, no gene has been shown to cause mesothelioma on its own without asbestos exposure. Moreover, blaming any hypothetical, non-existent issue with Mr. Perry's genes for the development of his mesothelioma is inapposite to South Carolina law. Even if there was a gene that contributed to his mesothelioma, Mr. Perry must be "taken as he is found." *Waring v. Johnson*, 533 S.E.2d 906, 912-913 (Ct.App. 2000) (citing *Raino v. Goodyear Tire and Rubber Co.*, 422 S.E.2d 98, 100 (1992)).

Dr. Diette's testimony will certainly not "assist the trier of fact to understand the evidence or determine a fact in issue." *Watson v. Ford Motor Co.*, 699 S.E.2d at 175. The consensus of the medical literature is that the BRCA 2 gene simply makes a person more susceptible to asbestos exposure. Dr. Diette's opinions ignore this fact. His opinions about germline mutations are not consistent with South Carolina law, will mislead and confuse the jury and should be struck.

III. Dr. Diette lacks an adequate foundation for his opinions that the talcum powder products at issue in these cases did not contain asbestos.

Dr. Diette offers the opinion that "Mr. Perry likely had no asbestos exposure from cosmetic talc produced and/or distributed by" Defendants.³⁰ He has not reviewed any materials specific to the asbestos content of the products at issue in this case, but has nevertheless concluded that "[b]ased on the available medical and scientific literature, it is not plausible that asbestos as a potential contaminant of cosmetic talc produced and/or distributed by Johnson & Johnson, Avon, Vi-Jon, Estée Lauder, Gold Bond, Ammens, IMI-Fabi, LLC, IMI Fabi (USA), LLC, and/or IMI-Fabi (Diana), could have caused Mr. Perry to develop pleural mesothelioma."³¹

³⁰ Ex 1, Diette Report, at 63.

³¹ Ex. 1, Diette Report, at 64.

In the *Payne* and *Plant* cases, Dr. Diette offered this same opinion on the basis of his reliance on the report of Alan Segrave to understand what talc mines were at issue.³² He was not aware of, and has never reviewed, any epidemiological studies for any talc mines³³:

5 Q. Are you aware of any epidemiology
6 studies performed on the miners and millers of
7 talc in Alabama?
8 A. I am not.
9 Q. Are you aware of any epidemiology
10 studies performed on the miners and millers of
11 talc in China?
12 A. Sure. I mean -- but there's
13 different epidemiology studies done in different
14 regions at different times.
15 Q. Are you aware of any specifically
16 done on miners and millers in China?
17 A. I can't recall -- I can't recall any
18 right now.
19 Q. Are you aware of any epidemiology
20 studies performed on the miners and millers of
21 talc in North Carolina?
22 A. I have not seen any.
23 Q. Are you aware of any epidemiology
24 studies performed on the miners and millers of
25 talc in Southwestern Montana?

1 A. I think I've seen, I've seen one
2 study that I think's an exposure study. But not
3 a traditional epidemiology study.
4 Q. So you're not aware of any
5 traditional epidemiology studies performed on
6 any miners and millers of talc in Southwestern
7 Montana?
8 A. Correct.

Moreover, Dr. Diette was questioned about his opinions being partially struck and/or limited before this very Court last year and he was asked if either his opinions or methodology to evaluate this had substantively changed.³⁴ Dr. Diette's response was: "*No, none. It's the same.*"³⁵ The reason for this is simple. There are no epidemiological studies of the talc miners and millers of these regions. The two pieces of evidence that would educate Dr. Diette about the asbestos

³² See *id.* at 22:22-23:4.

³³ See *id.* at 23:5-24:8.

³⁴ See Ex. 17, Deposition Transcript of Dr. Gregory Diette, dated July 3, 2024 at 19:9-20:2.

³⁵ See *id.* (emphasis added).

content of the products Mr. Perry used are testing of those products and epidemiological studies of the talc mines. Dr. Diette has reviewed neither. Therefore, Dr. Diette has no foundation to testify that any of the talcum powder products that Mr. Perry used did not contain asbestos.

V. Dr. Diette's testimony should be excluded under Rule 403 because it will confuse and mislead the jury.

Dr. Diette's opinions should also be excluded under Rule 403. That rule provides that relevant evidence may be excluded "if its probative value is substantially outweighed by the danger of unfair prejudice, confusion of the issues, or misleading the jury, or by considerations of undue delay, waste of time, or needless presentation of cumulative evidence." SCRE 403. Rule 403 should be applied to exclude overly prejudicial evidence offered by expert witnesses because, "[e]xpert evidence can be both powerful and quite misleading because of the difficulty in evaluating it." *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 595 (1993) (quoting Weinstein, *Rule 702 of the Federal Rules of Evidence is Sound; It Should Not Be Amended*, 138 F.R.D. 631, 632 (1991)) In fact, "[b]ecause of this risk, the judge in weighing possible prejudice against probative force under Rule 403 of the present rules exercises more control over experts than over lay witnesses." *Id.*

There is a substantial danger that Dr. Diette's testimony will confuse and mislead the jury. If the jury hears them discuss issues such as Mr. Perry's possible genetic defects, spontaneous mesothelioma, the purported lack of asbestos in the talcum powder products testified to by the Plaintiffs, and/or that the "worst case scenario" does not elevate Mr. Perry's risk of mesothelioma, the jury could be unreasonably swayed by the fact that experts are offering these opinions—although there is no foundation in the factual record for any of Dr. Diette's opinions on these subjects. The jury will be misled by this testimony. Dr. Diette's opinions should therefore be excluded under Rule 403 as confusing and misleading.

CONCLUSION

WHEREFORE the Plaintiff respectfully asks this Honorable Court to grant this motion and exclude or limit the testimony of Dr. Diette.

Respectfully submitted,

/s/ Charles W. Branham

Charles W. Branham, III (SC Bar No. 106178)

Rachel A. Gross (Admitted *Pro Hac Vice*)

DEAN OMAR BRANHAM SHIRLEY, LLP

302 N. Market Street, Suite 302

Dallas, TX 75202

T: 214-722-5990

rgross@dobslegal.com

Other email: tgilliland@dobslegal.com

Theile B. McVey (SC Bar No. 16682)

Jamie D. Rutkoski (SC Bar No. 103270)

KASSEL MCVEY ATTORNEYS AT LAW

1330 Laurel Street

Post Office Box 1476

Columbia, SC 29202-1476

T: 803-256-4242

tmcvey@kassellaw.com

jrutkoski@kassellaw.com

Other email: emoultrie@kassellaw.com

ATTORNEYS FOR PLAINTIFF

July 10, 2024

Dallas, TX

EXHIBIT 1

Gregory B. Diette, M.D., M.H.S.

27 June 2024

Gregory B. Diette, M.D., M.H.S.
8805 Columbia 100 Parkway
Suite 101
Columbia, Maryland 21045

Ms. Lucy Willson, Esq.
Willcox & Savage, PC
440 Monticello Avenue, Suite 2200
Norfolk, Virginia 23510

RE: Michael Perry v. Johnson & Johnson, *et al.*

Dear Ms. Willson,

This report has been prepared at your request as a summary of my opinions regarding claims that Mr. Michael Perry contracted pleural mesothelioma as a result of asbestos exposure.¹ Mr. Perry claimed that he was exposed to asbestos from occupational and non-occupational sources.²

I have reviewed the materials, in this case, to determine the potential role, if any, of talcum powder containing products from Johnson & Johnson (“Johnson’s Baby Powder” and “Shower to Shower”) that were allegedly purchased at Wal-Mart locations, Avon (“Avon Deep Woods,” “Avon Musk,” “Avon Spicy,” “Timeless,” “Soft Musk,” “Cotillion,” “Birds of Paradise,” and “Skin So Soft”), Vi-Jon (“Equate”), Estée Lauder Companies (“ELC” for “White Linen”), Gold Bond and Ammens products allegedly bottled by PTI Royston, and cosmetic talc allegedly produced by IMI-Fabi, LLC, IMI Fabi (USA), LLC and IMI Fabi (Diana) LLC allegedly containing asbestos, as a cause of Mr. Perry’s disease.

A list of case materials and literature relied upon may be found in Appendices A, B, and C.

¹ Summons and Complaint, p. 13.

² Summons and Complaint, p. 15-16, 26, 59-60.

PROFESSIONAL QUALIFICATIONS.

I am a physician licensed to practice in the State of Maryland and am Board Certified in pulmonary medicine and internal medicine. I am an attending physician at the Johns Hopkins Hospital and the Johns Hopkins Bayview Medical Center which includes outpatient and inpatient care. I am Professor in the Division of Pulmonary & Critical Care Medicine at The Johns Hopkins University School of Medicine. Additionally, I am Professor of Epidemiology and Environmental Health and Engineering in the Bloomberg School of Public Health at Johns Hopkins. My research is focused on the environmental causes of human diseases. I obtained my undergraduate degree from the University of Pennsylvania, my medical degree from Temple University, and my Master's in Epidemiology from Johns Hopkins University, School of Hygiene and Public Health. My residency training in internal medicine was at the Hospital of the University of Pennsylvania and Pulmonary Critical Care Fellowship was at Johns Hopkins Hospital.

BACKGROUND AND EMPLOYMENT HISTORY FOR MR. PERRY.**Background.**

Mr. Michael Perry was born on 20 December 1969 in Springfield, IL. In 1976 Mr. Perry moved with his family to a house in Springfield that was built on pastureland, where his family kept chickens and a large garden.³ Mr. Perry stated that his parents did not utilize chemicals, fertilizers, or pesticides on this property.⁴ He lived on a sailboat for spring breaks and summers during college and after he graduated he moved to the sailboat full time.⁵ Mr. Perry has lived in Charleston, South Carolina since 1996, and was living there at the time of his deposition in 2023. From approximately 2003 to 2020, he lived on a 15-acre horse farm and raised horses, cows, chickens, and goats.⁶

Mr. Perry's father was an aviation mechanic and inspector, working in the cockpit of planes at Springfield Capital Airport.⁷ At the time of Mr. Perry's deposition, his father was age 78 and had late-stage prostate cancer.⁸ Mr. Perry's mother was a computer programmer for Horace Mann

³ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 24; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 267-269; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 663.

⁴ Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 665, 668.

⁵ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 18-19, 24; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 267-270; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 459-461, 497; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 655-656, 677-678, 680, 682-683, 686.

⁶ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 23-24, 28, 76-77; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 271-273; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 457, 498; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 656-658, 667, 689.

⁷ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 22-23; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 284-285.

⁸ Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 250; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 865.

Insurance Co.⁹ She was diagnosed with “*uterl cancer*” [sic] that was discovered when she gave birth to Mr. Perry, she had a massive heart attack in 2007, and she died of small cell carcinoma lung cancer in 2010.^{10,11} Mr. Perry has an older sister named Michelle who is reportedly in good health, although he had not spoken to her in over twenty years.¹² Mr. Perry’s maternal grandmother died of colon cancer sometime prior to 2010.¹³ His maternal grandfather died of pancreatic cancer.¹⁴

Mr. Perry married his husband, Mr. Lonnie Long, in approximately 2006. Mr. Long is a retired realtor.¹⁵

Mr. Perry has a history of kidney stones, knee and hernia operations, lipoma removal from the back of his neck, and oral surgeries, such as root canals and tooth extractions.¹⁶ He had a partial colectomy in 2010, where nine inches of ascending colon was removed because of recurrent diverticulitis.¹⁷

Mr. Perry was diagnosed with COVID-19 in January 2023.¹⁸ After testing negative 14 days later, he had a persistent cough that worsened and he developed night sweats.¹⁹ He went to see his physician for an annual checkup and was told his labs were “*awful*.”²⁰ He was put on an antibiotic and steroid to rule out pneumonia.²¹ He received a chest x-ray which was “*a little hazy*” and was sent in for a CT scan with contrast on his lung.²² After receiving the results, he was sent to a thoracic surgeon who stated he could have mesothelioma, lung disease, or a noncancerous aggressive skin disease.²³ They performed a biopsy the following day (in July 2023) which, with pathology, confirmed a diagnosis of mesothelioma.²⁴

⁹ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 22-23; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 388.

¹⁰ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 54-56; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 249; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 865, 899.

¹¹ Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 865.

¹² Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 211, 250; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 505.

¹³ Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 249; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 427-428.

¹⁴ Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 249.

¹⁵ Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 192-193.

¹⁶ Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 327, 329.

¹⁷ Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 328; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 825.

¹⁸ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 147-148.

¹⁹ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 147-148.

²⁰ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 147-148.

²¹ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 147-148.

²² Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 149.

²³ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 150-151.

²⁴ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 150-151.

Employment History.

Mr. Perry graduated from Riverton High School in Springfield, IL in 1988 before attending and graduating from the University of Illinois with a degree in communications in 1993.²⁵ He then attended the College of Charleston where he sought a degree in finance and hotel management. He did not obtain a degree.²⁶

Mr. Perry and his sister “*walked beans and corn*” as a summer job in their rural farming community when they lived in the family home.²⁷

When Mr. Perry was 15 years old, in approximately 1985, he worked as a lifeguard at the Holiday Inn Holidome pool in Springfield, IL. He was ultimately promoted to resident manager.²⁸ He worked this job through college until he left around 1993.²⁹

Starting in 1989, Mr. Perry spent his spring and summer breaks as a sailboat operator, providing one-week charters through the Florida Keys and Bahamas for the general public before moving to the boat to continue this work full time from approximately 1993 through 1996.³⁰

After moving to South Carolina, Mr. Perry worked for Hilton Hotel Worldwide from 2000 to 2017, where he was a general manager and consultant, traveling to various hotel properties to ensure integrity and cleanliness.³¹ From 2017 to 2020, he was the general manager at Homewood Suites. In 2020, he started working as the general manager at Market Pavilion. He was on medical leave at the time of his deposition.³²

Social Security Records reflect earnings from various jobs reported on his behalf including country clubs, YMCA/YWCA, a farm supply store, Boy Scouts, a sporting goods store, insurance companies, other hotels or management companies, a pizza store, a clothing store, FedEx, transportation and leasing companies, and a baking company, however, no testimony was provided regarding these employments.³³

²⁵ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 19; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 196; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 445.

²⁶ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 19.

²⁷ Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 211.

²⁸ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 26-27; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 206-208, 274; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 840.

²⁹ Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 840.

³⁰ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 49-50; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 270, 356, 358; Videotaped Deposition of +Michael Perry, Vol III, taken 12 October 2023, p. 354-355, 497; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 719, 841.

³¹ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 52; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 276-278.

³² Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 282.

³³ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 5-11.

Work History Chart:

Approximate Dates	Employer (Location)	Title/Task	Claimed Asbestos Exposure
1985	Oakcrest Country Club (Springfield, IL) ³⁴	No testimony provided	Not specified
1985 to 1993	Holiday Inn “Holidome” (Springfield, IL) ³⁵	Lifeguard, management	Drywall, joint compound ³⁶
1986	Springfield Pleasure Driveway and Park District Bookkeeper (Springfield, IL) ³⁷	No testimony provided	Not specified.
1987	Illini Country Club (Springfield, IL) ³⁸	No testimony provided	Not specified
1987	Young Men’s Christian Assn of Springfield (Springfield, IL) ³⁹	No testimony provided	Not specified
1987 to 1991, 1994, 1997 to 2000	Raynor Hotel Co. (Dixon, IL) ⁴⁰	No testimony provided	Not specified
1987	MM&B Management Inc (Springfield, IL) ⁴¹	No testimony provided	Not specified
1987 to 1990	Springfield Park District (Springfield, IL) ⁴²	No testimony provided	Not specified
1988	Young Women’s Christian Association of Springfield (Springfield, IL) ⁴³	No testimony provided	Not specified
1989 to 1996	Midnight Dragon Boat Tours (Florida, Bahamas) ⁴⁴	Operator	None claimed.

³⁴ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1985 to 2000, p. 4.³⁵ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 127-129.³⁶ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 127-129; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 273; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 843-846, 877.³⁷ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1985 to 2000, p. 4.³⁸ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 5.³⁹ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 5.⁴⁰ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 6.⁴¹ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 6.⁴² Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 6.⁴³ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 6.⁴⁴ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 26-27, 49-50; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 197, 270, 354-356, 358; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 656.

Summary Report of Gregory B. Diette, M.D., M.H.S.

Approximate Dates	Employer (Location)	Title/Task	Claimed Asbestos Exposure
1989 to 1990	Farm Supply Services Inc (Springfield, IL) ⁴⁵	No testimony provided	Not specified
1990 to 1993	Boy Scouts of America (Irving, TX) ⁴⁶	No testimony provided	Not specified
1990 to 1992	Illini Sporting Goods Inc (Springfield, IL) ⁴⁷	No testimony provided	Not specified
1991	Adventures Underwater (Springfield, IL) ⁴⁸	No testimony provided	Not specified
1993	Vics Pizza Inc (Springfield, IL) ⁴⁹	No testimony provided	Not specified
1994	Lincoln Land FS Inc (Jacksonville, FL) ⁵⁰	No testimony provided	Not specified
1994	General Car & Truck Leasing System Inc (Davenport, IA) ⁵¹	No testimony provided	Not specified
1994 to 1995	Gap Inc (San Francisco, CA) ⁵²	No testimony provided	Not specified
1995 to 1996	Viacom Inc. (Torrance, CA) ⁵³	No testimony provided	Not specified
1996 to 1997	Springfield Enterprises Inc (Scottsdale, AZ) ⁵⁴	No testimony provided	Not specified
1996	Federal Express Corporation & Subsidiaries (Collierville, TN) ⁵⁵	No testimony provided	Not specified
1997	Metropolitan Life Insurance Co (Saint Louis, MO) ⁵⁶	No testimony provided	Not specified

⁴⁵ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 6.

⁴⁶ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 7.

⁴⁷ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 7.

⁴⁸ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 7.

⁴⁹ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 7.

⁵⁰ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 8.

⁵¹ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 8.

⁵² Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 8.

⁵³ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 8.

⁵⁴ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 8.

⁵⁵ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 9.

⁵⁶ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 9.

Summary Report of Gregory B. Diette, M.D., M.H.S.

Approximate Dates	Employer (Location)	Title/Task	Claimed Asbestos Exposure
2000	Bunch Transport Inc (Columbia, SC) ⁵⁷	No testimony provided	Not specified
2000 to 2009	Promus Operating LLC Sole MBR (Hilton Hotels) ⁵⁸ (Memphis, TN)	General Manager and Consultant	Drywall, joint compound ⁵⁹
2010	Aetna Life Insurance Company (Hartford, CT) ⁶⁰	No testimony provided	Not specified
2010 to 2011	Park Hotels & Resorts Inc (Tysons, VA) ⁶¹	General Manager and Consultant	Not Specified
2011 to 2015	City Market Hotel Associates LLC (Doubletree Guest Suites) ⁶² (Charleston, SC)	General Manager and Consultant	Drywall, joint compound ⁶³
2015 to 2016	Derst Baking Company (Savannah GA) ⁶⁴	No testimony provided	Not specified
2016 to 2020	Trinet HR II Inc (Lakewood Ranch, FL) ⁶⁵	No testimony provided	Not specified
2016	Oasis Outsourcing V Inc (West Palm Beach, FL) ⁶⁶	No testimony provided	Not specified
2017 to 2020	Homewood Suites (Mount Pleasant, SC) ⁶⁷	General Manager	Not specified
2020 to 2021	WHHG Mt. Pleasant Management LLC (Boston, MA) ⁶⁸	No testimony provided	Not specified

⁵⁷ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 9.

⁵⁸ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 9.

⁵⁹ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 129-130, 132-135; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 280; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 848, 850, 877.

⁶⁰ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 10.

⁶¹ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 10.

⁶² Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 10.

⁶³ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 132-133.

⁶⁴ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 10-11.

⁶⁵ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 11.

⁶⁶ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 11.

⁶⁷ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 24, 32, Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 282.

⁶⁸ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 11.

Approximate Dates	Employer (Location)	Title/Task	Claimed Asbestos Exposure
2021 to 2022	Aimbridge Employee Service Corp (Plano, TX) ⁶⁹	No testimony provided	Not specified
2022 to 2023	Market Pavilion Hotel Inc (Charleston, SC) ⁷⁰	General manager	Not specified

PLAINTIFF'S POTENTIAL ENCOUNTERS WITH ASBESTOS.

Occupational

From approximately 1985 through 1993, Mr. Perry worked as a lifeguard and as a general manager at a Holiday Inn Holidome in Springfield, IL, where renovations and repairs were completed in hotel rooms due to water damage, mold, and mildew from an indoor pool.⁷¹ He was present while this work was performed and witnessed people cutting sheetrock, taping joints, using compound, and dry sanding.⁷² He walked around with the general manager to check rooms for completion of work.⁷³ Mr. Perry testified there were no barriers in place as the work was completed and claimed there was drywall dust throughout the hotel.⁷⁴ He claimed drywall typically only lasted a few months in the pool area before it was replaced.⁷⁵

While working at Embassy Suites in Charleston, SC as a general manager from 2000 to 2001, Mr. Perry testified there was sheetrock replacement done due to water damage.⁷⁶ He alleged that he was in proximity to this work as it was completed, and he went to the rooms to verify the work was done properly after completion.⁷⁷

Mr. Perry testified that there was a library next to Embassy Suites that the hotel used for storage. The building was reportedly condemned by the county because it contained asbestos.⁷⁸ Mr. Perry reportedly entered the library “on a semi-regular basis” or possibly more than two times a month

⁶⁹ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 11.

⁷⁰ Social Security Administration - Itemized Statement of Earnings for Michael Perry – 1987 to 2023, p. 11.

⁷¹ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 127-128; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 273.

⁷² Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 843-845

⁷³ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 129; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 273; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 843.

⁷⁴ Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 844-845.

⁷⁵ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 127-128; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 845-846.

⁷⁶ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p.129-130; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 278; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 848.

⁷⁷ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 132; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 848.

⁷⁸ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 130-131; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 279-280; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 849.

to add or retrieve furniture for the hotel. He stated workers may have hit the ceiling while moving things “*because the ceilings were starting to cave in at that point in time.*”⁷⁹

During Mr. Perry’s time working as a general manager and consultant for Hilton Hotel Worldwide, he reportedly visited Hampton Inn in the early 2000s and oversaw sheetrock replacement following a flood that collapsed the ceilings of the first floor.⁸⁰ He testified he was required to take pictures of the damage and had to check every room after completion to verify the work was done properly before they reopened to guests.⁸¹ He claimed there was a “*white haze of sheetrock dust*” when he walked into the hotel.⁸²

From 2014 to 2017 or 2020, Mr. Perry worked at Homewood Suites in Mount Pleasant, SC where there was a construction defect in the ceiling of the lobby, causing it to collapse.⁸³ Workers ripped out the entire ceiling, and he was present while the work was done. He inspected the work following completion.⁸⁴

Mr. Perry claimed that work done at these properties left “*a chalk residue*” all over his body and believed he may have been exposed to asbestos at these jobs if any of the work was done with sheetrock or joint compound that contained asbestos.^{85,86,87}

Non-Occupational.

Mr. Perry reportedly had talcum powder applied to him or personally applied talcum powder to himself as part of his daily hygiene routine from approximately 1974 until 2019.^{88,89} He and his husband began reducing their powder usage prior to completely stopping in 2019.⁹⁰

Mr. Perry recalled his mother applied powder to him, from 1974 to 1976, after showering.⁹¹ He applied body powders to himself after showering beginning in 1976. He showered a minimum of two times each day, sometimes three times daily if it was hot outside, and he applied powder

⁷⁹ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 130-131; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 278-279.

⁸⁰ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 133-134; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 280; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 850.

⁸¹ Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 280.

⁸² Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 133-134.

⁸³ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 132-133; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 282.

⁸⁴ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 132-133.

⁸⁵ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 135; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 877.

⁸⁶ Summons and Complaint, p. 59-60.

⁸⁷ Plaintiffs’ Responses to Defendant’s Interrogatories, p. 3-4.

⁸⁸ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 34-35, 37, 93-94; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 290-293, 299, 307; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 423; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 750, 762

⁸⁹ Summons and Complaint, p. 16.

⁹⁰ Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 331

⁹¹ Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 289-291; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 463

after each shower.⁹² He used body powder multiple times a day on a daily basis and switched the powders he used, depending on what the day entailed.⁹³ He rotated using four or five different brands of “vanity” or fragrance powders from the 1980s through 2019 and he explained that he did not wear the same scent multiple days in a row.⁹⁴ He applied one brand of fragrance powder in his shoes while living on the sailboat.⁹⁵

Mr. Perry had talcum powder applied to him after each haircut every other week from the time he was a small child until approximately 2019.^{96,97}

While living on the sailboat, Mr. Perry occasionally applied powder to his hands, arms, and face to dry them before he entered the engine room.⁹⁸

Mr. Perry stated he occasionally had a “*dry powder fight*” with friends on the boat, which filled the area with powder, leading them to cough and sneeze.⁹⁹

Mr. Perry testified that he applied talcum powder to his hockey gear before putting it on when he played in the winter season (from approximately 1976 through the mid-1980s).¹⁰⁰

Mr. Perry was in close proximity to his mother as she applied powder after showering.^{101,102} She applied the powder to her hands or to a poof before applying it to her body.¹⁰³ She wore certain fragrance powders to work, out to dinner, or while entertaining.¹⁰⁴

Mr. Perry was responsible for cleaning the bathroom and other areas after powdering from the time he was a child until approximately 2019.¹⁰⁵

⁹² Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 59-61, 93-94; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 463; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 753-754, 757.

⁹³ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 59-60, 79-80,

⁹⁴ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 44-48, 51, 64, 79-80, 98-101; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 411-414; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 756, 802-803, 888-889, 894.

⁹⁵ Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 417.

⁹⁶ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 93-94; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 776, 782-783, 787-789, 791-793, 795-796, 798-799, 803-804.

⁹⁷ Summons and Complaint, p. 16.

⁹⁸ Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 892-893.

⁹⁹ Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 758.

¹⁰⁰ Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 203-204; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 802-803, 893

¹⁰¹ Summons and Complaint, p. 16.

¹⁰² Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 36, 53, 55-56, 66-68, 70-71, 83-84, 102-103; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 292-293, 380, 382, 387, 393; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 499, 506, 509; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 878-879, 881, 883-884, 899.

¹⁰³ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 70-72; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 472-473.

¹⁰⁴ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 83-85; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 386.

¹⁰⁵ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 63,74-77

Mr. Perry was in close proximity to his father when they both applied powder after fishing on weekends in the 1980s.^{106,107} His father also used talcum powder on himself for hygiene, however, Mr. Perry was not in close proximity to him while he applied it.¹⁰⁸

Mr. Perry believed he was exposed to asbestos when he performed brake work under his father's supervision "*more than six dozen times*" on two different family vehicles between 1984 and 1987, but specified that he considered each wheel its own separate job.^{109,110,111} This work included changing both drum and disc brakes, sanding or grinding the shoes on drum brakes, and blowing them out with his mouth or an air compressor.¹¹² Mr. Perry also broke down the engine and changed the head gaskets on both vehicles and replaced four rotors on two separate occasions.¹¹³

PLAINTIFF'S ENCOUNTERS WITH MATERIALS PRODUCED BY JOHNSON & JOHNSON.

Mr. Perry used Johnson & Johnson baby powder on a regular basis from 1974 to 2019 as a part of his daily routine after showering, sometimes multiple times a day.^{114,115} Mr. Perry's mother showered with him as a child five days a week until 1976 and he recalled his mother applying Johnson & Johnson baby powder and Shower to Shower to him after showering from 1974 to 1976.¹¹⁶ He began independently showering and applying powder to himself from 1976

¹⁰⁶ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 97; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 286; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 423-424

¹⁰⁷ Summons and Complaint, p. 16.

¹⁰⁸ Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 286; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 813-814.

¹⁰⁹ Plaintiffs' Responses to Defendant's Interrogatories, p. 3-4.

¹¹⁰ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 113-115, 122-123; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 239-240; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 592, 608; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 853, 877.

¹¹¹ Work History Affidavit, p. 1

¹¹² Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 116-120, 125-126; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 215-217, 225-227; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 621; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 860-861.

¹¹³ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 122-124; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 222; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 613-614.

¹¹⁴ Summons and Complaint, p. 16.

¹¹⁵ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 38-43, 79-80, 87, 89-90; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 299

¹¹⁶ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 111; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 289-291; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 463.

onwards.¹¹⁷ If Johnson & Johnson baby powder was not available, he used Shower to Shower. He recalled last using Shower to Shower prior to 2010, when his mother was still alive.¹¹⁸

Mr. Perry applied Johnson & Johnson baby powder to himself when he lived on a sailboat between 1989 and 1996, if he needed to work in the engine room.¹¹⁹

Mr. Perry used Johnson & Johnson baby powder in combination with one other brand of powder on his hockey gear prior to putting it on during the winter hockey season.¹²⁰ He applied Johnson & Johnson baby powder after swimming which he did year-round.¹²¹

Mr. Perry was in close proximity to his mother when she applied Johnson & Johnson baby powder and Shower to Shower to herself after showering five to seven days a week from 1974 to 1992 and once a month until 2007 or 2008.^{122,123,124}

Mr. Perry's sister applied Johnson & Johnson baby powder and Shower to Shower in the bathroom they shared in the family home, but he did not specifically see her applying it.¹²⁵

Mr. Perry and his husband alternated applying Johnson & Johnson baby powder with another brand of powder to each other after showering, possibly multiple times a day, from approximately 2002 through 2019.¹²⁶ He used Johnson & Johnson baby powder more frequently in the summer months.¹²⁷

PLAINTIFF'S ENCOUNTERS WITH MATERIALS PRODUCED BY AVON.

Mr. Perry's father reportedly used Avon Deep Woods, Avon Musk, and Avon Spicy talcum powders from approximately the 1970s until approximately 1984. Mr. Perry testified he did not see his father apply body powder. Mr. Perry's Plaintiff's Responses to Defendant's Interrogatories include claims that he was in close proximity to both of his parents while they

¹¹⁷ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 59-61, 93-94; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 307; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 463; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 753-754, 757.

¹¹⁸ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 111; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 317.

¹¹⁹ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 88-89.

¹²⁰ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 60; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 203-204.

¹²¹ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 60; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 203-204.

¹²² Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 53, 56-57, 66-68, 83-84, 102-103; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 508.

¹²³ Summons and Complaint, p. 16.

¹²⁴ Plaintiff's Responses to Defendant's Interrogatories, p. 4.

¹²⁵ Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 295.

¹²⁶ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 91; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 317-319, 344.

¹²⁷ Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 310.

applied body powders.^{128,129} Mr. Perry allegedly played with the Avon Deep Woods powder bottle in the 1970s.¹³⁰

Mr. Perry's mother allegedly used multiple Avon powders including Timeless, Soft Musk, Cotillion, Birds of Paradise, and Skin So Soft in his presence from approximately 1974 or 1975 to 2010.^{131,132,133} He witnessed her application of body powder approximately five to seven days a week from 1974 to 1992 and once a month from 1992 to 2010.¹³⁴ His mother also allegedly "poofed" his face with powder if he was "acting up."¹³⁵

PLAINTIFF'S ENCOUNTERS WITH MATERIALS PRODUCED BY VI-JON/EQUATE.

Mr. Perry and his husband alternated applying Equate powder with another brand of powder to each other after showering, possibly multiple times a day, from approximately 2002 through 2019.¹³⁶

PLAINTIFF'S ENCOUNTERS WITH MATERIALS PRODUCED BY ESTÉE LAUDER.

Mr. Perry was allegedly in close proximity to his mother when she applied White Linen as a part of her hygiene routine from the 1980s to the 1990s.^{137,138} She used this powder in addition to another brand of body powder.¹³⁹ Mr. Perry was in close proximity to his mother as she applied powder products at least five days a week after showering from 1974 or 1975 until approximately 1992, and then at least once a month from approximately 1992 until she died in 2010.¹⁴⁰

¹²⁸ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 73; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 484, 486-487, 489-492.

¹²⁹ Plaintiff's Responses to Defendant's Interrogatories, p. 4.

¹³⁰ Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 489.

¹³¹ Summons and Complaint, p. 16.

¹³² Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 53-54, 108, 110; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 466-473, 475-478, 481, 483.

¹³³ Plaintiff's Responses to Defendant's Interrogatories, p. 4.

¹³⁴ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 66-68, 83-84, 102-105.

¹³⁵ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 72; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 461-462.

¹³⁶ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 38, 91; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 317-319, 344.

¹³⁷ Summons and Complaint, p. 16.

¹³⁸ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 53, 56-57; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 430-432, 442.

¹³⁹ Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 442, 470-471.

¹⁴⁰ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 36, 53, 55-56, 66-68, 70-71, 83-84, 102-103; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 292-293, 380, 382, 387, 393; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 499, 506, 509; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 878-879, 881, 883-884, 899.

PLAINTIFF'S ENCOUNTERS WITH MATERIALS PRODUCED BY PTI ROYSTON (WITH RESPECT TO GOLD BOND AND AMMENS PRODUCTS).

Mr. Perry reportedly used medicated Gold Bond from approximately 1989 to 2019.^{141,142} From 1989 to 1993, he applied Gold Bond to his shoes.¹⁴³ During spring and summer breaks from 1989 to 1993 and full time from 1993 to 1996, he applied Gold Bond to his shoes, to his hands and face to dry off in the engine room.¹⁴⁴ He used Gold Bond in his boots or deck shoes when living on a farm in South Carolina.^{145,146} He testified that if he applied it to his feet, he massaged it in and did this multiple times per day.¹⁴⁷

Mr. Perry testified that he used Ammens medicated powder from the 1990s until the mid to late 2000s.¹⁴⁸ He reportedly used Ammens more frequently when he was living on the boat than on the farm.¹⁴⁹

PLAINTIFF'S ENCOUNTERS WITH MATERIALS PRODUCED BY IMI-FABI LLC.

Mr. Perry testified that he applied talcum powder to himself as part of his daily hygiene routine from approximately 1974 until 2019.^{150,151} Mr. Perry testified that he recalled his mother applied powder to him after showering from 1974 to 1976.¹⁵² He also testified that his barber applied talcum powder to him after his biweekly haircuts from the time he was a child until approximately 2019.^{153,154} Mr. Perry was in close proximity to his mother as she applied powder products at least five days a week from 1974 or 1975 until approximately 1992, and then approximately once a month from approximately 1992 until she died in 2010.^{155,156} Mr. Perry

¹⁴¹ Summons and Complaint, p. 16.

¹⁴² Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 43, 95-96; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 339-341, 356, 359; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 836-837.

¹⁴³ Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 356, 359.

¹⁴⁴ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 43, 95-96; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 339-340, 356.

¹⁴⁵ Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 339-340, 348.

¹⁴⁶ Summons and Complaint, p. 16.

¹⁴⁷ Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 341; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 836-837.

¹⁴⁸ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 47-49; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 419.

¹⁴⁹ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 49, 97.

¹⁵⁰ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 34-35, 37, 93-94; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 290-293, 299, 307; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 423; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 750, 762

¹⁵¹ Summons and Complaint, p. 16.

¹⁵² Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 289-291; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 463

¹⁵³ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 93-94; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 776, 782-783, 787-789, 791-793, 795-796, 798-799, 803-804.

¹⁵⁴ Summons and Complaint, p. 16.

¹⁵⁵ Summons and Complaint, p. 16.

¹⁵⁶ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 36, 53, 55-56, 66-68, 70-71, 83-84, 102-103; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 292-293, 380, 382, 387, 393;

testified that he was in close proximity to his father when they both applied powder after fishing on weekends in the 1980s.^{157,158}

Mr. Perry claims that he used or was in proximity to others' use of various brands of talcum powder products including Ammens, Avon, Calvin Klein, Cashmere Bouquet, Chanel, Clubman, Coty, Drakkar Noir, Estee Lauder, Gold Bond, Johnson and Johnson, Shower to Shower, Mennen, Old Spice, Pinaud, Polo Ralph Lauren, Stetson, Walgreens, Walmart, and White Linen.¹⁵⁹

TOBACCO HISTORY.

Mr. Perry was a nonsmoker.¹⁶⁰ His mother and father were smokers; he believed his father smoked less than one pack a day "*inside the home limitedly or in the garage.*"¹⁶¹

SELECTED MEDICAL DOCUMENTATION.

02.08.03 CT abd. The limited images of the lower thorax reveals no evidence of basilar lung disease, pleural or pericardial effusion. IMPRESSION: Focal inflammatory changes within the mesentery, left side of the abdomen adjacent to the left paracolic gutter. A small amount of fluid is seen in that region as well. There is no evidence of distinct mass or abscess.¹⁶²

02.08.03 AXR. Frontal projection of the chest demonstrates cardiomedial silhouette within normal limits. No evidence of acute pleural or parenchymal lung disease. No evidence of pneumothorax.¹⁶³

02.25.10 FINAL DIAGNOSIS: SIGMOID COLON, PARTIAL RESECTION:
DIVERTICULITIS. Microscopic Description: Sections of the grossly described diverticula demonstrate herniation of the mucosa through the muscularis and abutting the pericolic adipose tissue. Sections of the grossly described area of fat necrosis show a broad area of microabscess formation with histologic features consistent with prior perforation. Histologic features of mucosal dysplasia and malignancy are not identified. The surgical margins of resection show uninflamed, histologically viable tissue.¹⁶⁴

Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 499, 506, 509; Videotaped Deposition of Michael Perry, Vol IV, taken 13 October 2023, p. 878-879, 881, 883-884, 899.

¹⁵⁷ Videotaped Deposition of Michael Perry, Vol I, taken 10 October 2023, p. 97; Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 286; Videotaped Deposition of Michael Perry, Vol III, taken 12 October 2023, p. 423-424

¹⁵⁸ Summons and Complaint, p. 16.

¹⁵⁹ Summons and Complaint, p. 16.

¹⁶⁰ Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 249.

¹⁶¹ Videotaped Deposition of Michael Perry, Vol II, taken 11 October 2023, p. 256, 286-287.

¹⁶² CT abd 02.08.03 Radiology reports pg 1 thru 2 of 59.

¹⁶³ AXR 02.08.03 Radiology reports pg 4 of 59.

¹⁶⁴ Surgical Pathology Report 02.25.10 OCRPathology reports; 02.25.10..pdf 1 thru 2 of 6

- 12.27.11 Visit note. [Hiott] He still has reflux problems and uses Prevacid regularly. It is better since he lost some weight. Also, his asthma seems more related to his reflux so since that is better, his breathing is better and he has not had to use his inhaler.¹⁶⁵
- 06.06.12 Visit note. [Hiott] He also has reflux and is on Prevacid daily. As long as he takes this he doesn't have a problem with his asthma. He thinks his asthma is allergy and reflux-induced. He does take Allegra over-the-counter for his allergies.¹⁶⁶
- 06.24.13 Visit note. [Hiott] He does have underlying allergies but has not had to use the Allegra. His asthma has not flared as long as he keeps his reflux is ok. He does have reflux and uses generic Prevacid regularly. His reflux appears to be controlled. A/P: Asthma: Ventolin.¹⁶⁷
- 07.29.15 Visit note. [Hiott] He does uses Ventolin inhaler when he feels short of breath particularly when he goes from cold to the heat and hynidity [sic] outside. He has a history of acid reflux and has used over-the-counter lansoprazole. This has not been a problem recently. A/P: Asthma: Ventolin stable.¹⁶⁸
- 04.07.15 Operative Report. POSTOPERATIVE DIAGNOSIS: Left lower quadrant ventral hernia. OPERATIVE PROCEDURE: Laparoscopic left lower quadrant ventral hernia repair with a 6 x 7 cm Prolene mesh in the retrorectus position. Examination of the abdomen revealed a left lower quadrant small ventral hernia with some omentum in it.¹⁶⁹
- 12.27.16 Visit note. [Hiott] Patient does have allergies and will use over-the-counter Zyrtec or Allegra. Usually, spring and Fall are the worse. He does have asthma that is triggered by reflux and allergies. He has not had to use an inhaler recently because does [sic] have been controlled. A/P: Mild intermittent asthma without complication: stable, meds if needs has inhaler.¹⁷⁰
- 08.09.17 Colonoscopy Report. [Schnell, MD] Impressions: Moderate diverticulosis of the sigmoid colon¹⁷¹
- 05.12.17 Visit note. [Hiott] SORE THROAT. sometimes [sic] hard to swallow. feels [sic] lump in neck. Felt like a really sore throat, gland sore. Std for the last three months he starts coughing and can't stop. Clear mucas [sic]. He's concerned because his father recently was diagnosed with prostate cancer and there are other cancers in his family. A/P: Sore throat: Zithromax. Neck fullness: TSH, get US and if ok, send ENT.¹⁷²

¹⁶⁵ Visit note 12.27.11 PERRY ROPER 5.19.17-7.1.23 pg 205 thru 206 of 225.

¹⁶⁶ Visit note 06.06.12 PERRY ROPER 5.19.17-7.1.23 pg 203 thru 204 of 225.

¹⁶⁷ Visit note 06.24.13 PERRY ROPER 5.19.17-7.1.23 pg 199 thru 200 of 225.

¹⁶⁸ Visit note 07.29.15 PERRY ROPER 5.19.17-7.1.23 pg 182 thru 183 of 225.

¹⁶⁹ Operative report 04.07.15 OCRPERRY -RSFP ROPER 2022-2023.pdf 131 thru 132 of 265

¹⁷⁰ Visit note 12.27.16 PERRY ROPER 5.19.17-7.1.23 pg 176 thru 177 of 225.

¹⁷¹ Colonoscopy Report 08.09.17 OCRAdmission to Palmetto Digestive Health Specialists dated 08.09.17..pdf 1 thru 2 of 6

¹⁷² Visit note 05.12.17 PERRY ROPER 5.19.17-7.1.23 pg 174 thru 175 of 225.

- 06.11.17 CT Abdomen Pelvis. Lung bases: Minimal dependent atelectasis is seen at the lung bases. IMP: Acute diverticulitis of the midsigmoid colon without evidence of perforation or abscess formation.¹⁷³
- 06.20.19 Visit note. [Hiott] He has mild asthma and can use his albuterol inhaler as needed. He has not had a problem with that recently. ROS: Respiratory: Shortness of breath denies. Asthma admits, mild intermittent affected by allergies/GERD. A/P: Mild intermittent asthma without complication: Ventolin.¹⁷⁴
- 08.29.19 Visit note. [Hiott] HPI:49-year-old white male comes in today stating that he had fevers and had gone to the ER. His temperature was actually up to 102.7. He had no symptoms except a fever. No sore throat, sinus drainage, headache, dizziness, cough, nausea, vomiting, or diarrhea. At the ER his temperature was up and they did basic labs. Flu test and strep test were negative. They did a chest x-ray at the ER that was negative. He says he still feels funny and feels sweaty but his temperature will be normal. Temperature today is totally normal. ROS: Respiratory: Shortness of breath denies. Asthma admits, mild intermittent affected by allergies/GERD. Cough denies. Shortness of breath at rest denies. Shortness of breath with exertion denies. Wheezing denies. A/P: Fever. Follow Up: on labs.¹⁷⁵
- 12.19.19 Visit note. [Hiott] Patient has had a cold and a hacking cough. He's only been sick for about 4 days and discussed is probably viral. He's had some greenish mucus and if it doesn't get better next week let us know. He had a fever but it's okay today he says. ROS: Respiratory: Shortness of breath denies. Asthma admits, mild intermittent affected by allergies/GERD. A/P: Mild intermittent asthma without complication: Ventolin, stable. Viral upper respiratory tract infection: treat symptoms. monitor.¹⁷⁶
- 06.16.20 Visit note. [Hiott] Sts [sic] has been anxious with the covid19, and everything going on. sts in August he had fever that no one could figure out why. said he was very sick went to ER. No one could figure out what was causing fever. Hes wondering if he had covid 19. Fever went up to 104 and he missed 9 days of work. He does have allergies and has been having a lot of trouble with that recently. He gets really tight and short of breath and uses Ventolin inhaler. Does have low-grade asthma and has been on inhalers. If the allergies are better he probably won't need to use that as much. A/P: Mild intermittent asthma without complication: Ventolin. Allergic rhinitis, unspecified seasonality, unspecified trigger: Fluticasone Propionate, Montelukast.¹⁷⁷

¹⁷³ CT Abd Pelvis 06.11.17 Radiology reports; 06.11.17 pg 1 thru 3 of 7.

¹⁷⁴ Visit note 06.20.19 PERRY ROPER 5.19.17-7.1.23 pg 148 thru 150 of 225.

¹⁷⁵ Visit note 08.29.19 PERRY ROPER 5.19.17-7.1.23 pg 142 thru 145 of 225.

¹⁷⁶ Visit note 12.19.19 PERRY ROPER 5.19.17-7.1.23 pg 136 thru 138 of 225.

¹⁷⁷ Visit note 06.16.20 PERRY ROPER 5.19.17-7.1.23 pg 132 thru 135 of 225.

01.13.21 Virtual Visit. [Germinario, MD] Allergic rhinitis and mild intermittent asthma: Well-controlled on montelukast (as needed), fluticasone and ventolin (PRN). He uses his rescue inhaler when there are weather and temperature changes.¹⁷⁸

03.01.21 CT Abdomen pelvis. Lower Thorax: Unremarkable.¹⁷⁹

06.04.21 Progress note. [Germinario, MD] In November 2019 he was very sick, in Roper ER. He had fatigue, 104.7 F fever. He was told he had a virus, but it was unclear which one. No respiratory symptoms. He never ended up getting antibody tested. He wonders if he had Covid. Since then he gets waves of exhaustion, occasionally has to just go to bed. He never had these symptoms prior to this illness in November 2020. He does not feel depressed. He estimates an episode at least once per week, often multiple days per week. No obvious inciting triggers. No other symptoms besides just feeling totally weak and exhausted. No fevers or night sweats. No unintentional weight loss. Allergic rhinitis and mild intermittent asthma: Well-controlled on montelukast (as needed), fluticasone and ventolin (PRN). He uses his rescue inhaler when there are weather and temperature changes. 2. Fatigue, unspecified type – Etiology is unclear. He may have had a Covid illness, other viral illness such as Lyme or EBV. Continues to have waves of fatigue, will expand blood work.¹⁸⁰

06.16.23 Visit note. [Germinario] he had COVID back in January and since then has had a fairly consistent persistent cough which is only sometimes productive of sputum with some development of intermittent shortness of breath, dyspnea on exertion and wheezing. He did not seek medical attention for this as he thought it was just a postviral cough and then he thought some of the symptoms might of been asthma related or allergy related as the pollen season came on. The persistence of his symptoms, however, it is concerning to him. He is not sure if he is actually having fevers but oftentimes at night he will wake [sic] up to quite a sweaty bed, not fully she [sic] soaking but he describes significant sweating. This is fairly new over the past 3 months. He has furthermore had unintentional weight loss of 14 pounds over the past 6 months. He reports decreased appetite but no significant abdominal pain or nausea or vomiting. A/P: Chronic cough: XR CHEST. Mild intermittent asthma with exacerbation: doxycycline, prednisone. Microcytic anemia. Rectal bleeding. Leukocytosis, unspecified type. Thrombocytosis. Night sweats. Unintentional weight loss. His symptoms are concerning, his physical exam is reassuring. I like to begin treatment/work-up with a chest x-ray which she [sic] can get today, and I am going to start him on a steroid dose as well as coverage for an asthma exacerbation given the ongoing cough following his COVID infection. His lungs are clear to auscultation bilaterally, there might be some slight decreased lung sounds at the left base. ADDENDUM 06/19/23: CXR reviewed, new hilar mass/density noted on CXR. CT w/ contrast ordered for better characterization.¹⁸¹

¹⁷⁸ Virtual Visit 01.13.21 Perry, Michael - Roper St. Francis Healthcare (Medical Vol 1 01.11.21 - 07.12.23) pg 28 thru 31 of 305.

¹⁷⁹ CT abd pelvis 03.01.21 Perry, Michael - Roper Hospital (Medical 03.01.21 - 06.30.23) pg 27 thru 28 of 333.

¹⁸⁰ Progress note 06.04.21 Perry, Michael - Roper St. Francis Healthcare (Medical Vol 1 01.11.21 - 07.12.23) pg 61 thru 66 of 305.

¹⁸¹ Visit note 06.16.23 PERRY ROPER 5.19.17-7.1.23 pg 64 thru 84 of 225.

06.16.23 CXR. FINDINGS: Slight left pleural fluid is present, with lobular small pleural-based densities over the left lateral chest wall at its mid portion, all new compared to prior study. No pleural fluid is seen on the right. Cardiac silhouette is not enlarged. No pulmonary vascular congestion. Ill-defined increased density is seen over the left hilar region, new compared to the prior study, especially projecting inferior to the left hilum. Impression: New slight left pleural fluid with lobular left pleural densities laterally and with new abnormal soft tissue density overlying the left hilum suspicious for mass or adenopathy. Follow-up chest CT with IV contrast would be useful for further investigation.¹⁸²

06.21.23 Visit note. [Germinario] Since last visit, patient was treated with steroid and antibiotic. CXR was obtained showing new slight left pleural fluid with lobular left pleural densities laterally and with new abnormal soft tissue density overlying the left hilum suspicious for mass or adenopathy. This was discussed with patient over phone and a CT scan was ordered. CT was performed today. This showed numerous left sided pleural based lesions/deposits and enlarged left cardiophrenic lymphadenopathy. Findings are worrisome for malignancy. Recommended was further evaluation with tissue sampling. There was a small left pleural effusion. He is feeling a bit better, feels like his cough has improved. He reveals to me today that his mother has small cell carcinoma of the lung. A/P: Lung mass: Discussed findings with patient, concern for malignancy. Discussed that further diagnosis and treatment plan would be made with specialist. I have sent referral today to Dr. Kline for urgent appointment for further eval.¹⁸³

06.21.23 CT chest. Lymph nodes: Numerous enlarged cardiophrenic nodes nodes [sic] include an index node measuring 1.6 x 1.3 cm. Airways: Central airways are patent. Lungs/Pleura: Several pleural deposits in the left lung with index deposit measuring 2.8 x 0.9 cm along the lateral left upper lobe and index implant along the anterior left upper lobe measuring 2.5-1.3 cm. Small left pleural effusion with associated pleural deposits including the index deposit along the left posterior lower lobe measuring 4.5 x 1.3 cm. No pneumothorax. Impression: Numerous left-sided pleural-based lesions/deposits and enlarged left cardiophrenic lymphadenopathy. Findings are worrisome for malignancy. Recommend further evaluation with tissue sampling. Follow PET/CT may also be considered to optimize tissue sampling target. Small left pleural effusion, suspected malignant.¹⁸⁴

06.29.23 Visit note. [Kline] HPI: 53 y/o M never smoker with a PMH of asthma, chronic back pain. Mother had small cell lung cancer. He was seeing his PCP for chronic cough. Covid in January. Cough did not resolve. Treated with course of antibiotics and steroids. CXR revealed L pleural fluid with findings suspicious for mass or adenopathy on L. Subsequent chest CT revealed L sided pleural lesions and L pleural effusion. No history of known asbestos exposure. Reports recent weight loss and poor appetite. ROS: fever, fatigue, weakness, night sweats, change in appetite, weight change, cough, asthma. A/P: Pleural based nodules on left with small left pleural effusion. Concerning for malignancy

¹⁸² CXR 06.16.23 Radiology reports pg 14 of 59.

¹⁸³ Visit note 06.21.23 PERRY ROPER 5.19.17-7.1.23 pg 42 thru 63 of 225.

¹⁸⁴ CT chest 06.21.23 Radiology reports pg 15 of 59.

or aggressive benign disease. Plan for OR tomorrow for left thoracoscopy, pleural biopsies, PleurX catheter. No pleurodesis planned at this time in case he needs future intervention in chest.¹⁸⁵

06.30.23 Operative Note. [Kline, MD] Pre-Op Diagnosis: Pleural mass. Pleural effusion, left. Post-Op Diagnosis: Malignancy. Procedures: 1-Bronchoscopy. 2-Left thoracoscopic pleural biopsies. 3-Left pleurx catheter insertion. Findings: 1-Multiple fleshy masses on parietal pleural surface, and fewer on the visceral pleural surface. 2-Full lung expansion (no trapping). 3-Malignancy per Dr. Hannay at FS.¹⁸⁶

06.30.23 Surgical Pathology consultation report. Reported 7/5/2023. Diagnosis: A. PLEURA, LEFT, BIOPSIES: NON SMALL CELL MALIGNANCY, MOST COMPATIBLE WITH MALIGNANT MESOTHELIOMA. B. PLEURA, LEFT, BIOPSY FOR FROZEN SECTION: NON SMALL CELL MALIGNANCY, MOST COMPATIBLE WITH MALIGNANT MESOTHELIOMA. Microscopic description: A-B: Sections (including frozen section slides) demonstrate an infiltrative non-small cell malignancy comprised of moderate to markedly atypical cells arranged predominantly in infiltrative sheets with prominent nucleoli. Keratinization is absent. Gland formation is not identified. Overtly sarcomatoid differentiation or features of a high-grade sarcoma are not appreciated. To further differentiate the lineage of these malignant cells, a panel of qualitative immunohistochemical stains (with appropriate positive controls) was performed on block A2: Cytokeratin AE1/3: Positive, Cytokeratin 7: Positive, Cytokeratin 5/6: Positive, Calretinin: Positive, WT1: Positive, Desmin: Negative, PSA: Negative, CK20: Negative, SOX10: Negative, TTF-1: Negative. Overall, coexpression of cytokeratins and mesothelial markers favors mesothelioma with extensively epithelioid features. There is no evidence of a pulmonary non-small cell carcinoma or metastatic colorectal carcinoma. Despite the prominent nucleoli, findings argue against metastatic prostatic adenocarcinoma. There is no evidence of metastatic melanoma. The frozen section diagnosis is confirmed.¹⁸⁷

07.07.23 Visit note. [Lingerfelt] Hematology/oncology; CC: Left malignant pleural mesothelioma, epithelioid type. Oncologic history: 1. Patient with COVID-19 in early 2023 and persistent cough. 2. Chest x-ray 6/16/2023 with a small left pleural effusion. 3. CT chest 6/21/2023 with numerous left-sided pleural-based lesions/deposits and left cardiophrenic lymphadenopathy with a small left pleural effusion. 4. Left Pleurx, thoracoscopy and biopsy 6/30/2023 showing malignant mesothelioma, epithelioid subtype. HPI: Patient presents today for initial consultation regarding mesothelioma. He drains his left Pleurx every other day, noting decreased output recently as well as some associated pain. He denies known asbestos exposure. Lungs: Diminished breath sounds on the left. Mr. Perry is a pleasant 53-year-old Caucasian gentleman with malignant pleural mesothelioma, epithelioid type, diagnosed 6/30/2023 status post thoracoscopy with biopsy and Pleurx placement. CT of the chest 6/21/2023 raise concern for left cardiophrenic lymphadenopathy. Patient has at least stage II disease, unclear if resectable

¹⁸⁵ Visit note 06.29.23 PERRY ROPER 5.19.17-7.1.23 pg 25 thru 39 of 225.

¹⁸⁶ Operative Note 06.30.23 Admission to Roper Hospital dated 06.30.23 pg 10 thru 12 of 12.

¹⁸⁷ Surgical pathology consultation report 06.30.23 Pages from Perry Complaint 8-11-2023 pg 1 thru 2 of 2.

at this time. He also has mild hepatitis of unclear significance at this time. 1. Obtain PET/CT. 2. Referral to pulmonology for staging bronchoscopy/EBUS. 3. Present patient's case at multidisciplinary tumor conference. 4. Patient may warrant port placement. 5. Return to the office in 2 weeks for reassessment and review of the above-mentioned work-up. If she [sic] is a surgical candidate, could consider induction cisplatin plus pemetrexed. If not, would consider palliative ipilimumab plus nivolumab.¹⁸⁸

07.11.23 Visit note. [Rangel] Hematology/oncology; Diagnosis: Suspected Malignant Pleural Mesothelioma, Epithelioid. Prior Treatments: VATS Thoroscopy [sic] with Pleural biopsy and PleurX placement. HPI: presents to the thoracic oncology multidisciplinary clinic today for an initial consultation regarding his recently diagnosed malignant pleural mesothelioma. He saw Dr. Lungerfelt (Charleston Oncology Associates) on 7/7/2023. Plan was for PET/CT and pulmonology referred for mediastinal staging to determine resectability. He presents here for a second opinion. Today, he reports feeling "frail" but better since having the PleurX placed. He has been draining ~250cc every other day, and although still present his cough and chest tightness have improved. He reports 30 lb weight loss in the past 6 months with intentional dieting, along with metallic taste/poor appetite and some early satiety. He has had intermittent fevers and night sweats for 2 months. He does report a history of asbestos exposure while working at the old library/Hotel Bennet downtown, as well as talc exposure. A/P: Suspected Malignant Pleural Mesothelioma: As this is a very rare malignancy, we will plan to obtain his biopsy specimen for internal review/confirmation. PET/CT has also been ordered to complete staging. If this does prove to be epithelioid mesothelioma, I will discuss with Dr. Gibney whether he is a candidate for upfront resection vs neoadjuvant chemotherapy (cisplatin/pemetrexed).¹⁸⁹

07.11.23 Cardiothoracic Surgery Consult. [Ramsden/Gibney] He was seen at Roper by Dr. Kline and was taken to the OR 6/30/23 for a left VATS pleural biopsy and pleur-x placement. His pathology returned most compatible with mesothelioma, favor epithelioid. He presents today for a second opinion regarding his diagnosis and treatment. He has not yet had a PET/CT but is scheduled for one 7/18/23. Mr. Perry denies any direct asbestos exposure however he did use a lot of talc throughout his life as a swimmer. He also use to work at embassy suites adjacent to the old county library which apparently had a lot of asbestos in the walls. A/P: epithelioid mesothelioma of the left pleura. We still need to have his pathology reviewed and confirmed here at MUSC as well as complete molecular testing. He needs to complete his staging with his PET scan 7/18/23. Should this be an epithelioid mesothelioma and be low volume we would consider proceeding with a pleurectomy. Should it be any other sub type then surgical resection would not be part of his treatment regimen.¹⁹⁰

07.12.23 Surgical Pathology Consult Report. MUSC. Final Diagnosis: A) OUTSIDE CASE, SR23-3043 (6/30/23): A. PLEURA, LABELED AS "LEFT", BIOPSY: EPITHELIOID MESOTHELIOMA, SEE COMMENT. IMMUNOHISTOCHEMICAL STAINS

¹⁸⁸ Visit note 07.07.23 Office notes of Charleston Oncology pg 1 thru 6 of 6.

¹⁸⁹ Visit note 07.11.23 Office notes of Medical University of South Carolina (reverse chron) pg 121 thru 125 of 128.

¹⁹⁰ Cardiothoracic Surgery Consult 07.11.23 Perry, Michael - MUSC Medical University of S. Carolina (Medical 07.08.23 - 08.18.23 Vol 1) pg 21 thru 24 of 437.

(PERFORMED AT OUTSIDE INSTITUTION, AVAILABLE FOR REVIEW):
 CALRETININ: POSITIVE, CK5/6: POSITIVE, CK7: POSITIVE, AE1/AE3:
 POSITIVE, WT-1: POSITIVE, CD45: NEGATIVE, CK20: NEGATIVE, DESMIN:
 NEGATIVE, PSA: NEGATIVE, SOX-10: NEGATIVE, TTF-1: NEGATIVE.
 IMMUNOHISTOCHEMICAL STAINS (MUSC): P16: LOST IN CELLS OF
 INTEREST. BAP-1: INTACT. B. PLEURA, LABELED AS "LEFT", BIOPSY:
 EPITHELIOID MESOTHELIOMA, SEE COMMENT. COMMENT: The morphology
 and immunoprofile are consistent with epithelioid mesothelioma. Given the patient's
 young age, childhood asbestos exposure should be considered clinically.¹⁹¹

07.18.23 PET/CT. FINDINGS: Widespread hypermetabolic nodular left pleural thickening. For reference, there is a large retroaortic mass along the posterior aspect of the left lower lobe measuring up to 5.1 x 3.1 cm with a max SUV of 18.6. There is an ill-defined hypermetabolic soft tissue lesion between the left lateral fifth and sixth ribs with a max SUV of 5.8, also suggestive of disease involvement. Additionally, there are multiple hypermetabolic left paramediastinal and pericardial nodules as well as multiple left pericardiophrenic lymph nodes versus implants. For reference there is a left pericardiophrenic lesion measuring 2.1 x 1.7 cm with a max SUV of 14.8. Ill-defined hypermetabolic focus involving the left lateral seventh rib with a max SUV of 4.2. CT FINDINGS: THORAX: Small left pleural effusion with a left chest tube in place. Diffuse bronchial wall thickening. IMP: Widespread hypermetabolic nodular left pleural thickening with probable left paramediastinal, pericardial, and pericardiophrenic involvement. Additionally, a hypermetabolic chest wall lesion between the left lateral fifth and sixth ribs as well as a hypermetabolic focus in the left lateral seventh rib are also suspicious for disease involvement. Incidental small hiatal hernia with ill-defined hypermetabolic activity in the region of the distal thoracic esophagus, which is nonspecific and often associated with reflux esophagitis. Consider correlation with patient history and/or endoscopy for further evaluation. Extensive colonic diverticulosis with long segment hypermetabolic thickening throughout the rectum, which is nonspecific though may represent uncomplicated diverticulitis. Consider correlation with patient history and/or colonoscopy if not recently performed.¹⁹²

07.24.23 Procedure report. [Gilbert, DO] Procedure: 11. Flexible bronchoscopy with airway exam. 12. EBUS TBNA station 4R. 13. EBUS TBNA station 7. 14. EBUS TBNA station 11L. Pre-operative Diagnosis: 1. Mesothelioma. 2. Abnormal CT. Post-operative Diagnosis: Same. Procedure: The flex bronchoscope was introduced and the vocal cords appeared gross within normal limits. We entered the trachea which appeared grossly within normal limits, as did the main carina. The right mainstem, right upper lobe, bronchus intermedius, right middle and right lower lobe all appeared grossly within normal limits. The left mainstem, left upper and left lower all appeared grossly within normal limits.¹⁹³

07.24.23 FNA report. Specimens: A Lymph Node, 4R, Bronchoscopic Guided, Fine Needle

¹⁹¹ Surgical Pathology Consult Report 07.12.23 Pathology reports; 02.25.10. pg 4 thru 6 of 6.

¹⁹² FDG PET CT 07.18.23 Radiology reports pg 26 thru 29 of 59.

¹⁹³ Procedure report 07.24.23 Admission to Medical University of South Carolina dated 07.24.23 pg 1 thru 2 of 9.

Aspiration. Final Diagnosis: NEGATIVE FOR MALIGNANT CELLS. Additional Findings: Benign polymorphous lymphocytes.¹⁹⁴

07.24.23 FNA report. Specimens: A Lymph Node, Level 7, Bronchoscopic Guided, Fine Needle Aspiration. Final Diagnosis: NEGATIVE FOR MALIGNANT CELLS. Additional Findings: Mixed population of lymphocytes and bronchial epithelial cells are present with focal acute inflammation, minute fragments of cartilage, and blood. Cell block is scant with blood clot.¹⁹⁵

07.24.23 FNA report. Specimens: A Lymph Node, 11 L, Bronchoscopic Guided, Fine Needle Aspiration. Final Diagnosis: SPECIMEN IS UNSATISFACTORY FOR EVALUATION. Additional Findings: Predominantly blood with rare bronchial epithelial cells. Cell block shows blood clot with minute fragments of cartilage.¹⁹⁶

08.08.23 Operative Report. Pre-op diagnosis: Mesothelioma. Post-Op Diagnosis: Mesothelioma. Procedure: DECORTICATION, TOTAL. PLEURECTOMY, PARIETAL. DIAGNOSTIC BRONCHOSCOPY, RIGID OR FLEX. THORACENTESIS. CHEMOTHER, INTRACAVITARY, PLEURAL. EXCISION MALIGNANT LESION INCLUDING MARGINS, TRUNK, ARMS, OR LEGS; EXCISED DIAMETER 0.6 TO 1.0 CM. DIAPHRAGMATIC HERNIA REPAIR. THORACOTOMY WITH WEDGE RESECTION. Findings: moderate volume disease. Extended p/d with resection of portion of diaphragm with complex repair using patch. Complete macroscopic resection. Betadine heated therapy x 45 min. Excised previous port sites x 3, total diameter ~1 cm.¹⁹⁷

08.08.23 Surgical pathology report. Final Diagnosis: A. SOFT TISSUE, LABELED AS "TUMOR IMPLANT," EXCISION: EPITHELIOID MESOTHELIOMA. B. FIBROADIPOSE TISSUE, LABELED AS "PORT SITE #1," EXCISION: MESOTHELIOMA PRESENT IN INFLAMED SKIN AND SUBCUTANEOUS TISSUE. C. RIB, LABELED AS "6TH," RESECTION: ONE OF TWO LYMPH NODES WITH METASTATIC MESOTHELIOMA (1/2), BENIGN MUSCLE, BENIGN BONE WITH TRILINEAGE HEMATOPOIESIS. D. LYMPH NODE, LABELED AS "LEVEL 10," LYMPHADENECTOMY: ONE BENIGN LYMPH NODE (0/1). E. LYMPH NODES, LABELED AS "LEVEL 9," LYMPHADENECTOMY: THREE BENIGN LYMPH NODES (0/3), MESOTHELIOMA PRESENT IN SURROUNDING SOFT TISSUE. F. DIAPHRAGM, LABELED AS "IMPLANT," EXCISION: INVASIVE MESOTHELIOMA, MESOTHELIOMA INVOLVES A CAUTERIZED MARGIN, TRANSDIAPHRAGMATIC EXTENSION NOT IDENTIFIED. G. LYMPH NODES, LABELED AS "LEVEL 7," LYMPHADENECTOMY: FOUR BENIGN LYMPH NODES (0/4). H. LUNG, LABELED AS "LEFT LOWER LOBE," LOBECTOMY: LUNG TISSUE WITH INVASIVE MESOTHELIOMA INVOLVEMENT OF VISCERAL PLEURA, ONE OF ONE INTRAPARENCHYMAL LYMPH NODE POSITIVE FOR METASTATIC

¹⁹⁴ FNA report 07.24.23 Pathology reports pg 3 thru 4 of 18.

¹⁹⁵ FNA report 07.24.23 Pathology reports pg 5 thru 7 of 18.

¹⁹⁶ FNA report 07.24.23 Pathology reports pg 8 thru 10 of 18.

¹⁹⁷ Operative report 08.08.23 Admission to Medical University of South Carolina dated 080823 pg 9 thru 12 of 32.

MESOTHELIOMA (1/1), SURGICAL MARGINS NEGATIVE FOR MESOTHELIOMA. I. PLEURA, PLEURECTOMY: HISTOLOGIC TYPE: EPITHELIOID MESOTHELIOMA, HISTOLOGIC GRADE: HIGH GRADE (NUCLEAR ATYPIA SCORE: 2, MITOTIC COUNT SCORE: 3 (15 PER 2 MM²), NUCLEAR GRADE: 2, NECROSIS: PRESENT), TUMOR FOCALITY: DIFFUSE, TUMOR SITE: PARIETAL PLEURA, VISCERAL PLEURA, DIAPHRAGM, TUMOR SIZE: UNABLE TO BE DETERMINED, TUMOR EXTENT: DIFFUSE, INVOLVING LEFT LOWER LOBE, DIAPHRAGM, MARGIN STATUS: NEGATIVE IN THIS SPECIMEN, REGIONAL LYMPH NODE STATUS: UNINVOLVED BY INVASIVE MESOTHELIOMA (0/8), TREATMENT EFFECT: NO KNOWN PRESURGICAL THERAPY. J. LYMPH NODE. LABELED AS "LEVEL 5," LYMPHADENECTOMY: ONE BENIGN LYMPH NODE (0/1). K. SKIN, FIBROADIPOSE TISSUE, LABELED AS "PORT SITE #2," EXCISION: BENIGN SKIN WITH ACUTELY INFLAMED FIBROADIPOSE TISSUE WITH FIBROSIS. L. SKIN, FIBROADIPOSE TISSUE LABELED AS "PORT SITE #3," EXCISION: FOCAL MESOTHELIOMA PRESENT. PATHOLOGIC STAGE CLASSIFICATION (pTNM, AJCC 8TH EDITION): pT3 pN1, NUMBER OF LYMPH NODES EXAMINED: 12, NUMBER OF LYMPH NODES INVOLVED: 2. Synoptic Checklist: TUMOR – Tumor Focality: Diffuse, Tumor Site: Parietal pleura, Visceral pleura, Diaphragm, Tumor Size: Cannot be determined, Histologic Type: Epithelioid mesothelioma, Architectural Pattern: Tubulopapillary: 30 %, Solid: 70 %, Nuclear Atypia Score: 2 (moderate), Mitotic Count Score: 3 (high, 5 or more mitoses per 2 mm²), Nuclear Grade: 2, Necrosis: Present, Histologic Grade: High grade, Tumor Extent: Diaphragmatic muscle, Soft tissues of chest wall diffusely or in multiple foci, Treatment Effect: No known presurgical therapy. MARGINS – Margin Status: Mesothelioma present at margin, Margin(s) Involved by Mesothelioma: Diaphragm. REGIONAL LYMPH NODES - Regional Lymph Node Status: Tumor present in regional lymph node(s), Nodal Site(s) with Tumor: Bronchopulmonary: Intrapulmonary 6th rib soft tissue, Number of Lymph Nodes with Tumor: 2, Number of Lymph Nodes Examined: 12.¹⁹⁸

08.10.23 Op Note. [Gibney, DO] PREOPERATIVE DIAGNOSIS: Left chest Mesothelioma. POSTOPERATIVE DIAGNOSIS: Left chest Mesothelioma. PROCEDURE(S) PERFORMED: 1) Bronchoscopy with therapeutic aspiration of secretions, 2) Resection of left 6th rib, 3) left extended pleurectomy and decortication, 4) mediastinal lymph node dissection of stations 5, 7, 9. 5) Intraoperative heated betadine x 45 min, 6) multiple pneumorrhaphy, 7) left lower lobe wedge resections, 8) reconstruction of diaphragm, 9) excision of old incision sites <1cm diameter. INDICATIONS FOR PROCEDURE: The patient has biopsy proven, epithelioid [sic] mesothelioma with a PS of 0. The tumor did not harbor a BAP-1 mutation. He was offered resection with betadine. Procedure in Detail: The pleura was easy to come off the chest wall, and there was no obvious chest wall invasion. The tumor came off the diaphragm with the exception of the lateral portion. With the tumor free from the chest wall, it was noted that additional deposits were present in the pericardial fat and on the phrenic nerve. The nerve was sacrificed. Then, the visceral pleura was then mobilized off the lung. The tumor was passed as specimen. Multiple pneumorrhaphy and wedge resections of the left lower lobe

¹⁹⁸ Surgical pathology report 08.08.23 Pathology reports pg 11 thru 18 of 18.

performed for lung repair and removal of additional tumor deposits. toilet bronchoscopy [sic] was then performed - the carina was sharp, no endobronchial lesions and thin secretions primarily on the left were evacuated.¹⁹⁹

09.08.23 Visit note. [Lally] Radiation oncology: Presents for discussion for treatment options. Patient appears to be halfway through his chemotherapy. ASSESSMENT: Cancer Staging Malignant pleural mesothelioma. Staging form: Malignant Pleural Mesothelioma, AJCC 8th Edition. Pathologic: Stage IIIA (pT3, pN1, cM0). RECOMMENDATIONS: He is at high risk for disease progression. I will offer him radiation therapy to the left pleural space. I plan on using IMRT to deliver treatment.²⁰⁰

04.29.24 CT Chest. IMPRESSION: Similar postsurgical changes in the left chest with trace pleural effusion. Pleural thickening in the left upper medial chest is slightly prominent compared to 12/5/2023 and is nonspecific. Short-term follow-up CT would be helpful.²⁰¹

05.01.24 Oncology note. [Rangel, MD] Treated with IMRT to the Left Lung 45Gy/25fx from 2/8/2024- 3/14/2024. A/P: # Stage IIIA Malignant Pleural Mesothelioma, Pure Epithelioid: He has now been treated with 6 cycles of adjuvant Cisplatin and Pemetrexed from 9/13/23-12/27/2023. He saw Dr. Lally and completed IMRT which he tolerated relatively well. His interim CT Chest performed on 4/29/24 showed post-surgical changes and non-specific thickening in the medial LUL pleural which will be followed on surveillance scans.²⁰²

Radiology:

I have reviewed relevant radiological images of Mr. Perry. A detailed list of the studies received can be found in **Appendix C** at the conclusion of this report.

Past Medical History.

- Allergic rhinitis²⁰³
- Anxiety (2011)^{204,205}
- Asthma (triggered by GERD)^{206,207}

¹⁹⁹ Op Note 08.10.23 Perry, Michael - MUSC Medical University of S. Carolina (Medical 07.08.23 - 08.18.23 Vol 1) pg 316 thru 318 of 437.

²⁰⁰ Visit note 09.08.23 Office notes of Medical University of South Carolina (reverse chron) pg 78 thru 88 of 128.

²⁰¹ CT Chest 04.29.24 OCRRadiology reports; 12.05.23..pdf 3 of 4.

²⁰² Oncology note 05.01.24 OCROffice notes of Medical University of South Carolina (reverse chron)..pdf 10 thru 20 of 98.

²⁰³ Virtual Visit 01.13.21 Perry, Michael - Roper St. Francis Healthcare (Medical Vol 1 01.11.21 - 07.12.23) pg 28 thru 31 of 305.

²⁰⁴ Discharge summary 08.16.23 Admission to Medical University of South Carolina dated 080823 pg 1 thru 11 of 32.

²⁰⁵ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

²⁰⁶ Discharge summary 08.16.23 Admission to Medical University of South Carolina dated 080823 pg 1 thru 11 of 32.

²⁰⁷ Visit note 07.07.23 Office notes of Charleston Oncology pg 1 thru 6 of 6.

Summary Report of Gregory B. Diette, M.D., M.H.S.

- GERD²⁰⁸
- Diverticulitis s/p colectomy²⁰⁹
- Hyperlipidemia²¹⁰
- PTSD (2011)^{211,212}
- Covid (1/2023)²¹³
- Sigmoid diverticulosis and diverticular colitis (6/2023, 6/2017, 2001)^{214,215,216}
- Kidney stones²¹⁷
- Testicular cancer s/p orchiectomy and chemotherapy (1990)²¹⁸
- Lipoma scalp and neck²¹⁹
- Depression (2011)^{220,221}
- Microcytic anemia²²²
- Shingles, periorbital (2011)^{223,224}
- Skin lesion Lt wrist Junction Spitz's Nevus²²⁵
- Ruptured disc L4-L5 (1/2015)²²⁶
- Erectile dysfunction²²⁷
- Epididymal cyst²²⁸

²⁰⁸ Discharge summary 08.16.23 Admission to Medical University of South Carolina dated 080823 pg 1 thru 11 of 32.

²⁰⁹ Discharge summary 08.16.23 Admission to Medical University of South Carolina dated 080823 pg 1 thru 11 of 32.

²¹⁰ Virtual Visit 01.13.21 Perry, Michael - Roper St. Francis Healthcare (Medical Vol 1 01.11.21 - 07.12.23) pg 28 thru 31 of 305.

²¹¹ Discharge summary 08.16.23 Admission to Medical University of South Carolina dated 080823 pg 1 thru 11 of 32.

²¹² Visit note 07.07.23 Office notes of Charleston Oncology pg 1 thru 6 of 6.

²¹³ Discharge summary 08.16.23 Admission to Medical University of South Carolina dated 080823 pg 1 thru 11 of 32.

²¹⁴ Visit note 06.26.23 Admission to Palmetto Digestive Health Specialists dated 062623 pg 1 of 1.

²¹⁵ Visit note 06.21.23 PERRY ROPER 5.19.17-7.1.23 pg 42 thru 63 of 225.

²¹⁶ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

²¹⁷ Visit note 07.12.23 PERRY ROPER 5.19.17-7.1.23 pg 10 thru 24 of 225.

²¹⁸ Visit note 06.21.23 PERRY ROPER 5.19.17-7.1.23 pg 42 thru 63 of 225.

²¹⁹ Visit note 06.21.23 PERRY ROPER 5.19.17-7.1.23 pg 42 thru 63 of 225.

²²⁰ Visit note 06.16.23 PERRY ROPER 5.19.17-7.1.23 pg 64 thru 84 of 225.

²²¹ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

²²² Visit note 06.16.23 PERRY ROPER 5.19.17-7.1.23 pg 64 thru 84 of 225.

²²³ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

²²⁴ Visit note 10.05.19 PERRY ROPER 5.19.17-7.1.23 pg 139 thru 141 of 225.

²²⁵ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

²²⁶ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

²²⁷ Visit note 08.02.21 PERRY ROPER 5.19.17-7.1.23 pg 117 thru 118 of 225.

²²⁸ Visit note 08.13.19 PERRY ROPER 5.19.17-7.1.23 pg 146 thru 147 of 225.

- Precancerous skin lesions, sees dermatologist regularly²²⁹
- Mild aortoiliac atherosclerotic calcification²³⁰
- Benign thyroid cysts²³¹
- Coronary artery calcifications²³²
- Lipid poor hemangioma²³³
- Left pectoralis muscle lipoma²³⁴
- Polypoid mucosal thickening of the right maxillary sinus²³⁵
- Small hiatal hernia²³⁶
- Bilateral gynecomastia²³⁷
- Small fat-containing L inguinal hernia²³⁸
- Multifocal degenerative joint disease²³⁹
- Multicompartmental Tarlov cyst at S2/S2-3²⁴⁰
- Vitamin D deficiency²⁴¹

Past Surgical/Procedural History.

- Colectomy, laparoscopic sigmoid (3/2010)^{242,243,244}
- Left ventral hernia repair with mesh, laparoscopic (4/2015)^{245,246,247}
- Colonoscopy (6/2023)²⁴⁸

²²⁹ Visit note 12.27.11 PERRY ROPER 5.19.17-7.1.23 pg 205 thru 206 of 225.

²³⁰ CT Abdomen Pelvis w/o Contrast 03.01.21 PERRY ROPER 5.19.17-7.1.23 pg 217 of 225.

²³¹ US Thyroid 05.19.17 PERRY ROPER 5.19.17-7.1.23 pg 225 of 225.

²³² NM Lung Ventilation Perfusion VQ 07.14.23 Radiology reports pg 17 thru 19 of 59.

²³³ MRI Chest w/wo Contrast 07.17.23 Radiology reports pg 20 thru 22 of 59.

²³⁴ MRI Chest w/wo Contrast 07.17.23 Radiology reports pg 20 thru 22 of 59.

²³⁵ MRI brain w/wo Contrast 07.17.23 Radiology reports pg 23 thru 25 of 59.

²³⁶ FDG PET CT 07.18.23 Radiology reports pg 26 thru 29 of 59.

²³⁷ FDG PET CT 07.18.23 Radiology reports pg 26 thru 29 of 59.

²³⁸ FDG PET CT 07.18.23 Radiology reports pg 26 thru 29 of 59.

²³⁹ FDG PET CT 07.18.23 Radiology reports pg 26 thru 29 of 59.

²⁴⁰ MR sacrum PERRY -RSFP ROPER 2022-2023 pg 130 of 265.

²⁴¹ Progress note 06.28.22 Perry, Michael - Roper St. Francis Healthcare (Medical Vol 1 01.11.21 - 07.12.23) pg 164 thru 169 of 305.

²⁴² Discharge summary 08.16.23 Admission to Medical University of South Carolina dated 080823 pg 1 thru 11 of 32.

²⁴³ Visit note 07.07.23 Office notes of Charleston Oncology pg 1 thru 6 of 6.

²⁴⁴ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

²⁴⁵ Discharge summary 08.16.23 Admission to Medical University of South Carolina dated 080823 pg 1 thru 11 of 32.

²⁴⁶ Visit note 07.07.23 Office notes of Charleston Oncology pg 1 thru 6 of 6.

²⁴⁷ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

²⁴⁸ Visit note 07.07.23 Office notes of Charleston Oncology pg 1 thru 6 of 6.

- L4-S1 lumbar fusion (2017)²⁴⁹
- Bilateral inguinal hernia repair (2007)²⁵⁰
- Colonoscopy 8/9/2017, 2014²⁵¹ History of colonoscopy 2001, 2007²⁵² Orchiectomy for testicular cancer (1990)²⁵³
- Lipoma of neck excised²⁵⁴
- Colonoscopy (diverticulosis, repeat in 5 years; 9/2007)²⁵⁵
- Removed skin lesion left wrist (12/2010)²⁵⁶

Social History.

- No direct asbestos exposure^{257,258,259,260}
- Talc use throughout his life as a swimmer^{261,262}
- Worked at Embassy Suites adjacent to old county library which apparently had a lot of asbestos in the walls^{263,264}
- Married to male^{265,266}
- Never a smoker²⁶⁷
- No passive exposure to tobacco²⁶⁸
- No smokeless tobacco²⁶⁹

²⁴⁹ Visit note 07.07.23 Office notes of Charleston Oncology pg 1 thru 6 of 6.

²⁵⁰ Visit note 07.07.23 Office notes of Charleston Oncology pg 1 thru 6 of 6.

²⁵¹ GI note 04.10.19 Admission to Palmetto Digestive Health Specialists dated 04.10.19 pg 1 thru 2 of 2.

²⁵² H&P Cardiothoracic 06.29.23 Admission to Roper Hospital dated 06.30.23 pg 6 thru 10 of 12.

²⁵³ Visit note 06.21.23 PERRY ROPER 5.19.17-7.1.23 pg 42 thru 63 of 225.

²⁵⁴ Visit note 06.21.23 PERRY ROPER 5.19.17-7.1.23 pg 42 thru 63 of 225.

²⁵⁵ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

²⁵⁶ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

²⁵⁷ Discharge summary 08.16.23 Admission to Medical University of South Carolina dated 080823 pg 1 thru 11 of 32.

²⁵⁸ Visit note 07.07.23 Office notes of Charleston Oncology pg 1 thru 6 of 6.

²⁵⁹ Visit note 06.29.23 PERRY ROPER 5.19.17-7.1.23 pg 25 thru 39 of 225.

²⁶⁰ Visit note 07.11.23 Office notes of Medical University of South Carolina (reverse chron) pg 125 thru 128 of 128.

²⁶¹ Discharge summary 08.16.23 Admission to Medical University of South Carolina dated 080823 pg 1 thru 11 of 32.

²⁶² Visit note 07.11.23 Office notes of Medical University of South Carolina (reverse chron) pg 125 thru 128 of 128.

²⁶³ Discharge summary 08.16.23 Admission to Medical University of South Carolina dated 080823 pg 1 thru 11 of 32.

²⁶⁴ Visit note 07.11.23 Office notes of Medical University of South Carolina (reverse chron) pg 125 thru 128 of 128.

²⁶⁵ Discharge summary 08.16.23 Admission to Medical University of South Carolina dated 080823 pg 1 thru 11 of 32.

²⁶⁶ Visit note 07.07.23 Office notes of Charleston Oncology pg 1 thru 6 of 6.

²⁶⁷ Discharge summary 08.16.23 Admission to Medical University of South Carolina dated 080823 pg 1 thru 11 of 32.

²⁶⁸ Visit note 07.07.23 Office notes of Charleston Oncology pg 1 thru 6 of 6.

²⁶⁹ Visit note 07.07.23 Office notes of Charleston Oncology pg 1 thru 6 of 6.

Summary Report of Gregory B. Diette, M.D., M.H.S.

- No drug use²⁷⁰
- No alcohol use currently²⁷¹
- No children²⁷²
- College educated²⁷³
- Occupation: local developer²⁷⁴
- Engineer by trade²⁷⁵
- Works remotely for company doing sales and marketing²⁷⁶
- 1 dog²⁷⁷
- Travel in past 5 years (from 6/28/22) to Dominican Republic and South America²⁷⁸
- No caffeine²⁷⁹
- Diet: low fat, low cholesterol²⁸⁰
- Exercises 2-3 times per week²⁸¹
- Occupation: full-time Hotelier²⁸²
- No pets²⁸³
- Asbestos exposure while working at the old library/Hotel Bennet downtown²⁸⁴

Family History.

- Heart disease (mother)²⁸⁵
- Ovarian cancer (mother)²⁸⁶

²⁷⁰ Visit note 07.07.23 Office notes of Charleston Oncology pg 1 thru 6 of 6.

²⁷¹ Visit note 07.07.23 Office notes of Charleston Oncology pg 1 thru 6 of 6.

²⁷² Visit note 07.12.23 PERRY ROPER 5.19.17-7.1.23 pg 10 thru 24 of 225.

²⁷³ Visit note 07.12.23 PERRY ROPER 5.19.17-7.1.23 pg 10 thru 24 of 225.

²⁷⁴ Visit note 07.12.23 PERRY ROPER 5.19.17-7.1.23 pg 10 thru 24 of 225.

²⁷⁵ Visit note 06.21.23 PERRY ROPER 5.19.17-7.1.23 pg 42 thru 63 of 225.

²⁷⁶ Visit note 06.21.23 PERRY ROPER 5.19.17-7.1.23 pg 42 thru 63 of 225.

²⁷⁷ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

²⁷⁸ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

²⁷⁹ Visit note 09.09.16 PERRY ROPER 5.19.17-7.1.23 pg 178 thru 179 of 225.

²⁸⁰ Visit note 09.09.16 PERRY ROPER 5.19.17-7.1.23 pg 178 thru 179 of 225.

²⁸¹ Visit note 09.09.16 PERRY ROPER 5.19.17-7.1.23 pg 178 thru 179 of 225.

²⁸² Visit note 09.09.16 PERRY ROPER 5.19.17-7.1.23 pg 178 thru 179 of 225.

²⁸³ Visit note 09.09.16 PERRY ROPER 5.19.17-7.1.23 pg 178 thru 179 of 225.

²⁸⁴ Visit note 07.11.23 Office notes of Medical University of South Carolina (reverse chron) pg 121 thru 125 of 128.

²⁸⁵ Discharge summary 08.16.23 Admission to Medical University of South Carolina dated 080823 pg 1 thru 11 of 32.

²⁸⁶ Discharge summary 08.16.23 Admission to Medical University of South Carolina dated 080823 pg 1 thru 11 of 32.

Summary Report of Gregory B. Diette, M.D., M.H.S.

- Breast cancer (mother, paternal aunt)^{287,288}
- Prostate cancer (father)²⁸⁹
- Lung cancer, small cell (mother)^{290,291}
- Coronary artery disease (mother, paternal grandfather)^{292,293}
- Elevated lipids (father)²⁹⁴
- MI (mother, paternal grandfather, maternal grandfather, paternal aunt, maternal uncle)²⁹⁵
- Uterine cancer (mother)²⁹⁶
- Mesothelioma (paternal grandfather)²⁹⁷
- Liver cancer (maternal grandfather)²⁹⁸
- Colon cancer (maternal grandmother)²⁹⁹
- Aortic valve issues (non-specific)³⁰⁰
- Aortic aneurysm (father, grandmother)³⁰¹
- His uncle was recently diagnosed with lung cancer³⁰²

²⁸⁷ Discharge summary 08.16.23 Admission to Medical University of South Carolina dated 080823 pg 1 thru 11 of 32.

²⁸⁸ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

²⁸⁹ Discharge summary 08.16.23 Admission to Medical University of South Carolina dated 080823 pg 1 thru 11 of 32.

²⁹⁰ Visit note 07.07.23 Office notes of Charleston Oncology pg 1 thru 6 of 6.

²⁹¹ Visit note 06.29.23 PERRY ROPER 5.19.17-7.1.23 pg 25 thru 39 of 225.

²⁹² Visit note 07.07.23 Office notes of Charleston Oncology pg 1 thru 6 of 6.

²⁹³ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

²⁹⁴ Visit note 07.07.23 Office notes of Charleston Oncology pg 1 thru 6 of 6.

²⁹⁵ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

²⁹⁶ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

²⁹⁷ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

²⁹⁸ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

²⁹⁹ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

³⁰⁰ Visit note 06.28.22 PERRY ROPER 5.19.17-7.1.23 pg 104 thru 109 of 225.

³⁰¹ Visit note 02.25.19 PERRY ROPER 5.19.17-7.1.23 pg 159 thru 161 of 225.

³⁰² Palliative Care note 03.27.24 OCROffice notes of Medical University of South Carolina (reverse chron)..pdf 24 thru 34 of 98.

SCIENTIFIC AND MEDICAL LITERATURE REVIEW.**Scientific Principles.**

Epidemiologists and other scientists are often tasked with determining whether or not an exposure can cause an illness or condition. After an association has been demonstrated, criteria articulated by Austin Bradford Hill are often employed and considered the gold standard for assessing causation. Once an association has been established, these criteria to establish a causal inference include: consistency, strength of association, specificity, dose-response relationship, temporality, biologic plausibility, coherence of the association, and experimentation. Available evidence can be assessed and graded according to its sufficiency (or lack thereof) to establish a causal link. Evidence typically comes from research studies that involve humans, but can also include studies of animals or in vitro systems (toxicological and experimental) to provide supportive evidence, especially for plausibility.³⁰³

It is useful, when assessing causation, to consider non-causal explanations for the results of individual studies.³⁰⁴ These other explanations can come from bias, confounding, and chance. These limitations can be quite important, as they can lead to risk estimates that are falsely higher or lower than the actual risk, and they can even lead to conclusions that an exposure causes disease when it does not, and vice versa. Such limitations regarding asbestos literature have been described as:

- *“Limitations in air measurements and other data available for characterizing historical exposures;*
- *Limitations in the manner that the character of exposure (i.e., the mineralogical types of fibers and the range and distribution of fiber dimensions) was delineated;*
- *Limitations in the accuracy of mortality determinations or incompleteness in the extent of tracing of cohort members;*
- *Limitations in the adequacy of the match between cohort subjects and the selected control population; and*
- *Inadequate characterization of confounding factors, such as smoking histories for individual workers.”³⁰⁵*

With regard to human studies, there is also a hierarchy of evidence to consider. For example, clinical trials are often considered the strongest type of evidence, followed by observational

³⁰³ Hill AB. “The Environment and Disease: Association or Causation?” *Proceedings of the Royal Society of Medicine*. 1965;58:295-300.

³⁰⁴ Elwood JM. “The diagnosis of causation.” Chapter 8 in *Causal Relationships in Medicine: A Practical System for Critical Appraisal*. (New York, NY: Oxford University Press, 1988). 163-182.

³⁰⁵ Berman DW, Crump KS. “Final Draft: Technical Support Document for a Protocol to Assess Asbestos-Related Risk.” Environmental Protection Agency, 2003: EPA# 9345.4-06.

cohort and case control studies. The lowest quality of evidence comes from case reports, case series, and descriptive studies, which cannot demonstrate causation.³⁰⁶

There are recent examples of case series, in which authors have erroneously stated that they have found a causal relationship between an exposure and cancer. Emory et al. report on 75 plaintiff cases, in which they served as expert witnesses and reported their medico-legal conclusions that mesothelioma was caused by asbestos in cosmetic talc.^{307,308} Moline et al. similarly claims that their series of medico-legal plaintiff cases demonstrated causation.^{309,310,311} Dragani published a paper in 2020 that discusses the difficulty of determining the real cause of a particular cancer in an individual.³¹² Case reports and case series do not establish causation.

DIFFERENCES BETWEEN ASBESTOS AND TALC.

Asbestos.

Asbestos is a term that is used to describe several naturally occurring silicate mineral species when they are present in a fibrous form. Fibrous asbestos (known as asbestiform) has had commercial uses owing to certain physical properties including flexibility, separability, and weavability, as well as resistance to chemical and physical degradation. The major forms of commercial asbestos are known as amphibole and serpentine.³¹³ Certain industrial exposures to asbestos (e.g., amphibole-containing pipe insulation among insulators) are known causes of mesothelioma and lung cancer.³¹⁴

Talc.

Talc refers to a type of mineral, as well as to industrial mineral products that contain talc. Talc is not asbestos. It occurs naturally in many regions of the world. Its commercial use is attributable to properties of softness, platyness, inertness, and ability to absorb organic matter. When talc

³⁰⁶ Elwood JM. "The diagnosis of causation." Chapter 8 in *Causal Relationships in Medicine: A Practical System for Critical Appraisal*. (New York, NY: Oxford University Press, 1988). 163-182.

³⁰⁷ Emory TS, Maddox JC, and Kradin RL. "Malignant mesothelioma following repeated exposures to cosmetic talc: A case series of 75 patients." *American Journal of Industrial Medicine*. 2020;63(6):484-489.

³⁰⁸ Geyer SJ. "Evidence Does Not Support Exposure to Cosmetic Talc as Cause of Malignant Mesothelioma." *Journal of Occupational and Environmental Medicine*. 2020;62(2):e83-e84.

³⁰⁹ Moline J, Bevilacqua K, Alexandri M, Gordon RE. "Mesothelioma Associated with the Use of Cosmetic Talc." *Journal of Occupational and Environmental Medicine*. 2020;62(1):11-17.

³¹⁰ Geyer SJ. "Evidence Does Not Support Exposure to Cosmetic Talc as Cause of Malignant Mesothelioma." *Journal of Occupational and Environmental Medicine*. 2020;62(2):e83-e84.

³¹¹ Moline J, Bevilacqua K, Gordon RE. "Authors' Response to 'Evidence Does Not Support Exposure to Cosmetic Talc as a Cause of Malignant Mesothelioma.'" *Journal of Occupational and Environmental Medicine*. 2020;62(2):e85-e86.

³¹² Dragani TA. "Difficulties in establishing a causal link between chemical exposures and cancer cannot be overcome by court assessments." *Human and Experimental Toxicology*. 2020;39(8):1095-1107

³¹³ Institute of Medicine (US). "Background Information on Asbestos," Chapter 3 in *Asbestos: Selected Cancers*. Committee on Asbestos: Selected Health Effects, Board on Population Health and Public Health Practices, Institute of Medicine of the National Academies. The National Academies Press (US). Washington, DC; 2006. 49-62.

³¹⁴ Selikoff IJ, Seidman H. "Asbestos-associated deaths among insulation workers in the United States and Canada, 1967-1987." *Annals of the New York Academy of Sciences*. 1991;643:1-14.

particles are inhaled, it does not cause cancer in humans. Specifically, talc does not cause mesothelioma or lung cancer.³¹⁵

DIFFUSE PLEURAL THICKENING.

Diffuse pleural thickening refers to fibrosis of the lining of the chest wall and the lung. Diffuse pleural thickening is recognized on chest imaging. On CT scanning, it characteristically extends over 25 percent of the chest wall and obliterates the costophrenic sulci. CT criteria to define diffuse pleural thickening include: 1) the pleural thickening extends more than 8 cm in the craniocaudal direction; 2) the pleural thickening extends along more than 5 cm of the chest wall when visualized in cross-section, and 3) the pleural thickness exceeds 3 mm.

Diffuse pleural thickening often occurs from inflammation, as occurs with infection. There are other causes that include cancer, medications, radiation, trauma, environmental exposure (including asbestos and silica), bleeding, and treatment for tuberculosis.^{316,317}

PLEURAL PLAQUES.

Pleural plaques are circumscribed areas of fibrous thickening that typically involve the parietal pleura. They are typically bilateral and most commonly found along the sixth to ninth ribs and along the diaphragm. They may or may not be calcified. Calcifications are identified by CT scan in 50% of cases and morphological examination in 80%. These plaques can result from low level asbestos exposures from work-related, household, or environmental sources. Approximately 60% of persons with work-related asbestos exposure have pleural plaques on low dose CT. Pleural plaques are benign, usually asymptomatic, are not a type of cancer, and do not become cancer.^{318,319,320,321} In the example photos below, a normal image is on the left, and the image on the right shows an example of a patient with bilateral calcified pleural plaques.

³¹⁵ International Agency for Research on Cancer (IARC). "Carbon Black, Titanium Dioxide, and Talc." *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. World Health Organization, 2010: Volume 93.

³¹⁶ Stark P. "Imaging of pleural plaques, thickening and tumors." *UpToDate*. Last updated: 03 November 2017.

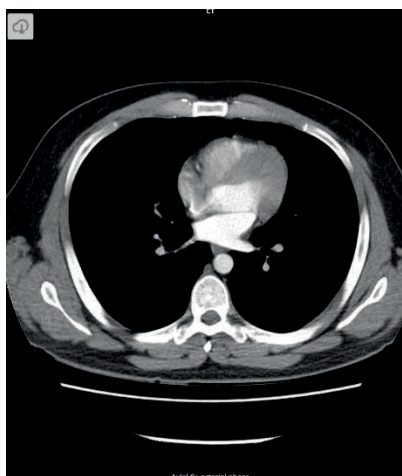
³¹⁷ Moon EK, Litzkey LA, Sterman DH. "Malignant Mesothelioma and Other Primary Pleural Tumors." Chapter 79 in *Fishman's Pulmonary Diseases and Disorders*, 5th ed. (McGraw-Hill Education, 2015).

³¹⁸ King TE Jr., "Asbestos-related pleuropulmonary disease." *UpToDate*. Last updated: 14 November 2018.

³¹⁹ Cowie RL, Becklake MR. "Pneumoconioses." In: Murray JF and Nadel JA, eds. *Textbook of Respiratory Medicine*. 6th ed. Philadelphia, PA: Elsevier Saunders; 2016.

³²⁰ Churg A. "Asbestos-Related Disease in the Workplace and the Environment: Controversial Issues." Chapter 3 in *The Lung: Current Concepts*. Edited by Churg A, Katzenstein ALA. (Baltimore, MD: Williams & Wilkins, 1993), 54-77.

³²¹ American Thoracic Society (ATS). "Diagnosis and Initial Management of Nonmalignant Disease Related to Asbestos." *American Journal of Respiratory and Critical Care Medicine*. 2004;170:691-715.



Normal CT of the chest performed with intravenous contrast. Scan during the arterial phase. 322



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ASBESTOSIS.

Asbestosis is a pneumoconiosis that is caused by inhalation of asbestos fibers. A pneumoconiosis is a lung disease caused by inhaling dust. The development of asbestosis requires high exposure to asbestos and is usually found in workers with many years of high exposure, such as asbestos miners and millers, asbestos textile workers, and asbestos insulators.³²⁴ A minimal exposure of 25 f/cc-yrs has been estimated to be needed to cause asbestosis.³²⁵ Asbestosis causes a restrictive lung problem that arises from an interstitial or fibrotic disease. Restriction can be assessed with pulmonary function tests and interstitial lung disease can be recognized by chest imaging and on biopsy specimens. “Clinical diagnosis depends on establishing the presence, extent and nature of pulmonary fibrosis and that the exposure has been of a duration and intensity sufficient to put the individual at risk for developing asbestosis.”^{326,327} Diagnosis of asbestosis also requires the exclusion of other diagnoses that would explain the pulmonary fibrosis. When there is uncertainty about the diagnosis, lung tissue from a surgical lung biopsy is needed to confirm the diagnosis. Symptoms of asbestosis typically include cough and shortness of breath, and a

³²² Case courtesy of Dr. Andrew Dixon, Radiopaedia.org, rID: 36676.

³²³ Stark P. “Imaging of pleural plaques, thickening and tumors.” *UpToDate*. Last updated: 03 November 2017.

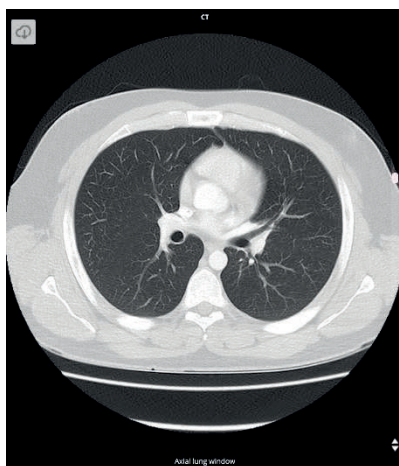
³²⁴ Churg A. “Asbestos-Related Disease in the Workplace and the Environment: Controversial Issues.” Chapter 3 in *The Lung: Current Concepts*, edited by Churg A, Katzenstein ALA. (Baltimore, MD: Williams & Wilkins, 1993), 54-77.

³²⁵ Churg A. “Asbestos-Related Disease in the Workplace and the Environment: Controversial Issues.” Chapter 3 in *The Lung: Current Concepts*, edited by Churg A, Katzenstein ALA. (Baltimore, MD: Williams & Wilkins, 1993), 54-77.

³²⁶ Cowie RL, Murray J, Becklake M. “Pneumoconioses and Other Mineral Dust-Related Diseases.” In *Murray and Nadel’s Textbook of Respiratory Medicine, 5th ed.* Edited by Mason RJ, et al. (Philadelphia, PA: Saunders, 2010). 1554-1586.

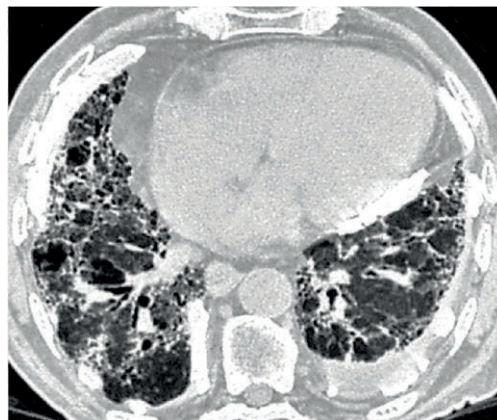
³²⁷ Selman M, Morrison LD, Noble PW, King Jr. TE. “Idiopathic Interstitial Pneumonias.” Chapter 57 in *Murray and Nadel’s Textbook of Respiratory Medicine, 5th ed.* Edited by Robert J. Mason, et al. (Philadelphia, PA: Saunders, 2010). 1356-1397.

common physical exam finding is inspiratory crackles.^{328,329,330} The example image on the left below shows normal lungs, and the example image on the right shows findings of asbestosis.



Normal CT of the chest performed with intravenous contrast. Scan during the arterial phase.

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CAUSES OF MESOTHELIOMA.

While many cases of mesothelioma can be linked to heavy industrial exposures to asbestos, there are also cases of mesothelioma for which there was no significant asbestos exposure. Other causes of mesothelioma include exposure to radiation, thorotrast, chronic inflammation, after treatment for tuberculosis, erionite-type zeolite, fluoro-edenite, and probably

³²⁸ American Thoracic Society (ATS). "Diagnosis and Initial Management of Nonmalignant Disease Related to Asbestos." *American Journal of Respiratory and Critical Care Medicine*. 2004;170:691-715.

³²⁹ Cowie RL, Murray J, Becklake M. "Pneumoconioses and Other Mineral Dust-Related Diseases." In *Murray and Nadel's Textbook of Respiratory Medicine, 5th ed.* Edited by Mason RJ, et al. (Philadelphia, PA: Saunders, 2010). 1554-1586.

³³⁰ Selman M, Morrison LD, Noble PW, King Jr. TE. "Idiopathic Interstitial Pneumonias." Chapter 57 in *Murray and Nadel's Textbook of Respiratory Medicine, 5th ed.* Edited by Robert J. Mason, et al. (Philadelphia, PA: Saunders, 2010). 1356-1397.

³³¹ Case courtesy of Dr. Andrew Dixon, Radiopaedia.org, rID: 36676.

³³² Stark P. "Imaging of occupational lung diseases." *UpToDate*. Last updated: 06 November 2020.

balangeroite.^{333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360}

As concluded by Andrion et al., “because asbestos fibers may be found in the lungs of the vast

³³³ Attanoos RL, Churg A, Galateau-Salle F, Gibbs AR, Roggli VL. “Malignant Mesothelioma and Its Non-Asbestos Causes.” *Archives of Pathology & Laboratory Medicine*. 2018;142(6):753-760.

³³⁴ Sporn TA, Roggli VL. “Mesothelioma.” Chapter 5 in *Pathology of Asbestos-Associated Diseases, 2nd ed.*, edited by Victor L. Roggli, et al. (New York, NY: Springer-Verlag, 2004), 104-168.

³³⁵ Pelnar PV. “Further Evidence of Nonasbestos-related Mesothelioma. A Review of the Literature.” *Scandinavian Journal of Work and Environmental Health*. 1988;14:141-144.

³³⁶ Peterson Jr. JT, Greenberg SD, Buffler PA. “Non-asbestos-related Malignant Mesothelioma. A Review.” *Cancer*. 1984;54:951-960.

³³⁷ Carbone M, Adusumilli P, Alexander R, et al “Mesothelioma: Scientific Clues for Prevention, Diagnosis, and Therapy.” *American Cancer Society, CA: A Cancer Journal for Clinicians*. 2019;69(5):402-429.

³³⁸ Kliment CR, Clemens K, Oury TD. “North American Erionite-Associated Mesothelioma with Pleural Plaques and Pulmonary Fibrosis: A Case Report.” *International Journal of Experimental Pathology*. 2009;2:407-410.

³³⁹ Oczypok EA, Sanchez MS, Van Orden DR, Berry GJ, Pourtabib, et al. “Case Report: Erionite-associated malignant pleural mesothelioma in Mexico.” *International Journal of Experimental Pathology*. 2016;9(5):5722-5732.

³⁴⁰ Ortega-Guerrero MA, Carrasco-Nunez G. “Environmental occurrence, origin, physical and geochemical properties, and carcinogenic potential of erionite near San Miguel de Allende, Mexico.” *Environmental Geochemical Health*. 2014;36:517-529.

³⁴¹ Ortega-Guerrero MA, Carrasco-Nunez G, Berragan-Campos H, and Ortega MR. “High incidence of lung cancer and malignant mesothelioma linked to erionite fibre exposure in a rural community in Central Mexico.” *Occupational Environmental Medicine*. 2015;72:216-218.

³⁴² Attanoos RL, Churg A, Galateau-Salle F, Gibbs AR, Roggli VL. “Malignant Mesothelioma and Its Non-Asbestos Causes.” *Archives of Pathology & Laboratory Medicine*. 2018;142(6):753-760.

³⁴³ Ilgren EB, Brena MO, Larragoitia JC, Navarrete GL, Brena AF, et al. “A Reconnaissance Study of a Potential Emerging Mexican Mesothelioma Epidemic due to Fibrous Zeolite Exposure.” *Indoor Built Environment*. 2008;17(6):496-515.

³⁴⁴ Maltoni C, Minardi F, Morisi L. “Pleural Mesotheliomas in Sprague- Dawley Rats by Erionite: First Experimental Evidence.” *Environmental Research*. 1982;29:238-244.

³⁴⁵ Carbone M, Ly BH, Dodson RF, et al. “Malignant Mesothelioma: Facts, Myths, and Hypotheses.” *Journal of Cellular Physiology*. 2012;227:44-58.

³⁴⁶ Jasani B, Gibbs A. “Mesothelioma Not Associated With Asbestos Exposure.” *Archives of Pathology & Laboratory Medicine*. 2012;136(3):262-267.

³⁴⁷ Hill RJ, Edwards RE, Carthew P. “Early changes in the pleural mesothelium following intrapleural inoculation of the mineral fibre erionite and the subsequent development of mesotheliomas.” *Journal of Environmental Pathology*. 1990;71:105-118.

³⁴⁸ Dikensoy O. “Mesothelioma due to environmental exposure to erionite in Turkey.” *Current Opinions in Pulmonary Medicine*. 2008;14:322-325.

³⁴⁹ Carbone M, Baris YI, Bertino P, Brass B, Comertpay S, et al. “Erionite exposure in North Dakota and Turkish villages with mesothelioma.” *Proceedings of the National Academy of Sciences*. 2011;108(33):13619-13623.

³⁵⁰ International Agency for Research on Cancer (IARC). “Arsenic, Metals, Fibres, and Dusts.” *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, World Health Organization. 2012: Volume 100C.

³⁵¹ Carbone M, Ly BH, Dodson RF. “Malignant Mesothelioma: Facts, Myths and Hypotheses.” *Journal of Cellular Physiology*. 2012;227(1):44-58.

³⁵² Mino JS, Montero R, Pigalarga R, et al. “Diffuse malignant epithelioid mesothelioma in a background of benign multicystic peritoneal mesothelioma: a case report and review of the literature.” *BMJ Case Report*. 2014; published online:1-3.

³⁵³ Butnor KJ, Pavlisko EN, Sporn TA, Roggli VL. “Malignant peritoneal mesothelioma and Crohn disease.” *Journal of Clinical Pathology*. 2017;70(3):228-232.

³⁵⁴ Butnor KJ, Rueckert J, Pavlisko EN, et al. “Malignant peritoneal mesothelioma in patients with endometriosis.” *Journal of Clinical Pathology*. 2018;71:971-974.

³⁵⁵ Bani-Hani KE and Gharaibeh KA. “Malignant Peritoneal Mesothelioma.” *Journal of Surgical Oncology*. 2005;91:17-25.

majority of individuals living in industrialized countries one must be exceedingly cautious in establishing a cause and effect relationship between the mineral and the disease.”³⁶¹

Certain occupations have an elevated risk of mesothelioma, including pipe coverers and insulators. Some occupations have not been associated with an elevated risk of mesothelioma, including nurses and other health care workers, hairdressers, and barbers.^{362,363,364,365,366,367,368,369,370,371,372,373,374,375}

Investigators suspect that there are predisposing factors in some people that allow cancer to develop. In a study by Ascoli et al., the authors listed evidence for the role of predisposing risk

³⁵⁶ Ishak GE, Khoury NJ, Birjawi GA, et al. “Imaging finding of familial Mediterranean fever.” *Clinical Imaging*. 2006;30:153-159.

³⁵⁷ Hershcovici T, Chajek-Shaul T, Hasin T, et al. “Familial Mediterranean Fever and Peritoneal Malignant Mesothelioma: A Possible Association?” *The Israel Medical Association Journal*. 2006;8:509-511.

³⁵⁸ Saebo A, Elgjo K, and Lassen J. “Could Development of Malignant Mesothelioma be Induced by Yersinia enterocolitica Infection?” *Medical Hypotheses*. 1993;40:275-277.

³⁵⁹ Valdivielso Cortazar E, Echeverria AM, Fernandez-Urien I, et al. “Peritoneal mesothelioma unmasked by an acute appendicitis.” *Scientific Letters*. 2016;39:217-218.

³⁶⁰ Wilkinson L, De P, Bloxham C. “Mesothelial reaction in longstanding Crohn’s ileitis simulating papillary mesothelioma.” *Journal of Clinical Pathology*. 2008;61:1119-1121.

³⁶¹ Andrion A, Bosia S, Paoletti L, et al. “Malignant Peritoneal Mesothelioma in a 17-year-old Boy with Evidence of Previous Exposure to Chrysotile and Tremolite Asbestos.” *Human Pathology*. 1994;25:617-622.

³⁶² Tucker PG, ed. “Who is at risk of exposure to asbestos?” In: *Case Studies in Environmental Medicine: Asbestos Toxicity*. ATSDR; 2000:30-39.

³⁶³ Peto J, Rake C, Gilham C, Hatch J. “Occupational, domestic and environmental mesothelioma risks in Britain. A case-control study.” *Health and Safety Executive (HSE), RR969 Research Report*. 2009.

³⁶⁴ Burnett C, Maurer J, and Dosemeci M. “Mortality by Occupation, Industry, and Cause of Death: 24 Reporting States, 1984-1988.” *U.S. Department of Health and Human Services*. 1997.

³⁶⁵ Andersen A, Barlow L, Engleland A, et al. “Work-related cancer in the Nordic countries.” *Scandinavian Journal on Work and Environmental Health*. 1995;25(suppl 2):116p.

³⁶⁶ Bouchardy C, Schuler G, Mider C, et al. “Cancer risk by occupation and socioeconomic group among men – a study by The Association of Swiss Cancer Registries.” *Scandinavian Journal on Work and Environmental Health*. 2002;28(1):1-88.

³⁶⁷ Lie JS, Kjaerheim. “Cancer risk among female nurses: a literature review.” *European Journal of Cancer Prevention*. 2003;12:517-526.

³⁶⁸ Lie JS, Andersen A, Kjaerheim K. “Cancer risk among 43,000 Norwegian nurses.” *Scandinavian Journal Work Environmental*. 2007;33(1):66-73.

³⁶⁹ McElvenny DM, Darnton AJ, Price MJ, et al. “Mesothelioma mortality in Great Britain from 1968 to 2001.” *Occupational Medicine*. 2005;55:79-87.

³⁷⁰ Milham S. “Occupational Mortality in Washington State: 1950-1989.” *U.S. Department of Health and Human Services*. Order No. 00913725. 1997.

³⁷¹ Olsen JH, Jensen OM. “Occupation and Risk of Cancer in Denmark: An analysis of 93,810 cancer cases, 1970-1979.” *Scandinavian Journal on Work and Environmental Health*. 1987;13(suppl 1):91p.

³⁷² Swanson GM, Burns PB. “Cancer Incidence Among Women in the Workplace: A Study of the Association Between Occupation and Industry and 11 Cancer Sites.” *Journal of Occupational and Environmental Medicine*. 1995;37(3):282-287.

³⁷³ Teschke K, Morgan MS, Checkoway H, et al. “Mesothelioma Surveillance to Locate Sources of Exposure to Asbestos.” *Canadian Journal of Public Health*. 1997;88(3):163-168.

³⁷⁴ Pukkala E, Martinsen JI, Lynge E, et al. “Occupation and cancer – follow-up of 15 million people in five Nordic countries.” *Acta Oncologica*. 2009;48(5):646-790.

³⁷⁵ Lewis RC, Smith SJ, Krevanko CF, et al. “Occupational exposure to cosmetic talc and mesothelioma in barbers, hairdressers, and cosmetologists: A systematic review of the epidemiology.” *Toxicology and Industrial Health*. 2023;39(10):564-582.

factors for mesothelioma, including that mesothelioma patients are more likely than controls to have a family history of cancer, subjects with certain combinations of genetic defects are at higher risk of mesothelioma, and clusters of the disease have occurred among blood relatives. Several studies have examined familial clustering of mesothelioma.³⁷⁶ These studies have provided evidence in some cases that there are shared heavy exposures, but in others, there is not a compelling exposure history, which suggests genetic susceptibilities.^{377,378,379} Genetic mechanisms that have been implicated in the development of malignant mesothelioma include, but are not limited to, germline BRCA1 associated protein-1 (BAP-1) inactivation syndrome, structural gene rearrangements in Ewing sarcoma breakpoint region 1 (EWSR1), or fused in sarcoma (FUS) and anaplastic lymphoma kinase (ALK) rearrangements.³⁸⁰ In a study by Panou et al.³⁸¹ of a series of patients with mesothelioma, they found that 12% had germline cancer susceptibility genes that included 13 different genes, some of which had not previously been identified [THEM127, CHEK2, MRE11A, VHL, WT1, and SDHA]. In this same study, the investigators found that cancer susceptibility genes were more common in people with minimal to no asbestos exposure, those who were younger, and those who had a second cancer.³⁸²

In another study by Panou et al., the authors identified numerous pathogenic or likely pathogenic germline mutations associated with malignant mesothelioma. Associated cancers included cancer of the breast, ovary, prostate, colon, pancreas, lung, brain, stomach, head and neck, bladder, liver, uterus, as well as melanoma, non-melanoma skin cancer, renal cell cancer, lymphoma, leukemia, cholangiocarcinoma, osteosarcoma, Wilm's tumor, rhabdomyosarcoma, glioma, adrenocortical carcinoma, and others.³⁸³ In a paper by Betti et al.,³⁸⁴ the authors listed eleven genes, besides BAP-1, involved in predisposition to malignant mesothelioma, including CDKN2A, PALB2, BRCA1, FANCI, ATM, SLX4, BRCA2, FANCC, FANCF, PMS1, and XPC. Another study³⁸⁵ estimated the frequency of germline mutations in cancer susceptibility genes in malignant mesothelioma. Compared to controls without cancer, there was a significantly higher risk of carrying a BRCA2 mutation in those with mesothelioma [OR 5: 95% CI 1.0-14.7, $p=0.03$]. The authors noted that the prevalence of germline cancer susceptibility gene mutations in patients with mesothelioma were “*strikingly similar to the proportion found in other solid*

³⁷⁶ Ascoli V, Cavone D, Merler E, et al. “Mesothelioma in blood related subjects: Report of 11 clusters among 1954 Italy cases and review of the literature.” *American Journal of Industrial Medicine*. 2007;50(5):357-369.

³⁷⁷ Lynch HT, Katz D, Markvicka SE. “Familial mesothelioma: review and family study.” *Cancer Genetics and Cytogenetics*. 1985;15:25-35.

³⁷⁸ Ascoli V, Cavone D, Merler E, et al. “Mesothelioma in blood related subjects: Report of 11 clusters among 1954 Italy cases and review of the literature.” *American Journal of Industrial Medicine*. 2007;50(5):357-369.

³⁷⁹ Picklesimer AH, Zanagnolo V, Niemann TH, et al. “Case report: Malignant peritoneal mesothelioma in two siblings.” *Gynecologic Oncology*. 2005;99(2):512-516.

³⁸⁰ Hung YP, Dong F, Watkins JC, et al. “Identification of ALK Rearrangements in Malignant Peritoneal Mesothelioma.” *Journal of the American Medical Association Oncology*. 2018;4(2):235-238.

³⁸¹ Panou V, Gadiraji M, Wolin A, et al. “Frequency of Germline Mutations in Cancer Susceptibility Genes in Malignant Mesothelioma.” *Journal of Clinical Oncology*. 2018;36(28):2863-2871.

³⁸² Panou V, Gadiraji M, Wolin A, et al. “Frequency of Germline Mutations in Cancer Susceptibility Genes in Malignant Mesothelioma.” *Journal of Clinical Oncology*. 2018;36(28):2863-2871.

³⁸³ Panou V, Røe OD. “Inherited genetic mutations and polymorphisms in malignant mesothelioma: A comprehensive review.” *International Journal of Molecular Sciences*. 2020;21(4327):1-17.

³⁸⁴ Betti M, Aspesi A, Sculco M, et al. “Genetic Predisposition for Malignant Mesothelioma: A concise review.” *Mutation Research-Reviews in Mutation Research*. 2019;781:1-10.

³⁸⁵ Panou V, Gadiraji M, Wolin A, et al. “Frequency of Germline Mutations in Cancer Susceptibility Genes in Malignant Mesothelioma.” *Journal of Clinical Oncology*. 2018;36(28):2863-2871.

tumors, including ovarian, colon, metastatic prostate cancer, and diverse advanced solid tumors.” Clinical characteristics associated with germline mutations included having minimal-to-no asbestos exposure (the most significant predictor) as well as young age and having a second cancer. A study examined 432 patients from the University of Chicago and the National Cancer Institute and found that loss of function mutations was more common in mesothelioma patients than controls.³⁸⁶ The mutations were found in BAP1, BRCA2, CHEK2, MLH1, MRE11A, PALB2, and POT1. Significant associations were found for BRCA2 gene mutations [OR 2.80 (95% CI: 1.02, 7.66, p 0.036)] and [OR 5.67 (95% CI: 1.82, 17.65, p 0.0007)]. Additional studies have found BRCA2 gene mutations in association with mesothelioma.^{387,388,389}

The Ataxia-telangiectasia-mutated (ATM) gene is a tumor suppressor gene that encodes a serine/threonine protein kinase involved in the repair and regulation of cellular pathways.³⁹⁰ Pleural mesothelioma has been described in a child with a mutation in the ATM gene who had no history of asbestos exposure,³⁹¹ as well as in an infant who was homozygous for ATM mutations.³⁹² In a case series,³⁹³ 14 “asbestos-exposed” people with malignant mesothelioma underwent whole genome sequencing. Ten people had cancer-related genes identified, including several genes involved in DNA repair. ATM was one of the genes identified in one person. A case series in Italy examined 93 pleural mesothelioma patients who lived in areas with past “high asbestos exposure.”³⁹⁴ ATM was one of the ten pathogenic truncating variants (PTVs) identified that are involved in DNA repair. A calculated estimate of asbestos exposure was lower in those with PTVs, than in those without PTVs, which suggested to the authors that those with a PTV may develop mesothelioma after lower exposures.³⁹⁵

Many types of tumors have been found in association with the BAP-1 mutation, including lung cancer, breast cancer, ovarian cancer, renal carcinoma, non-melanoma skin cancer (including basal cell and squamous), gastric cancer, meningioma, cholangiocarcinoma, leiomyosarcoma, neuroendocrine tumors, pancreatic cancer, paraganglioma, malignant fibrous histiocytoma,

³⁸⁶ Hassan R, Morrow B, Thomas A, et al. “Inherited predisposition to malignant mesothelioma and overall survival following platinum chemotherapy.” *The Proceedings of the National Academy of Sciences*. 2019;116(18):9008-9013.

³⁸⁷ Bertelsen B, Tuxen I, Yde, C, et al. “High frequency of pathogenic germline variants within homologous recombination repair in patients with advanced cancer.” *Genomic Medicine*. 2019;4(13):1-11.

³⁸⁸ Cheung M, Kadariya Y, Sementino E, Testa JR, et al. “Novel LRRK2 mutations and other rare, non-BAP1-related candidate tumor predisposition gene variants in high-risk cancer families with mesothelioma and other tumors.” *Human Molecular Genetics*. 2021;30(18):1750-1761.

³⁸⁹ Guo R, DuBoff M, Jayakumaran, et al. “Novel germline mutations in DNA repair in patients with malignant pleural mesothelioma.” *Journal of Thoracic Oncology*. 2019;15(4):650-660.

³⁹⁰ Sokolova A, Johnstone KJ, McCart Reed AE, et al. “Hereditary breast cancer: syndromes, tumour pathology and molecular testing.” *Histopathology*. 2023;82(1):70-82.

³⁹¹ Rosas-Salazar C, Gunawardena SW, Spahr JE. “Malignant Pleural Mesothelioma in a Child With Ataxia–Telangiectasia.” *Pediatric Pulmonology*. 2013;48:94-97.

³⁹² Mijalovsky A, Halperin D, Perez Y, et al. “Malignant Peritoneal Mesothelioma in an Infant With Familial ATM Mutations.” *Journal of Pediatric Hematology/Oncology*. 2018;40(8):e511-e515.

³⁹³ Cheung M, Kadariya Y, Sementino E, Testa JR, et al. “Novel LRRK2 mutations and other rare, non-BAP1-related candidate tumor predisposition gene variants in high-risk cancer families with mesothelioma and other tumors.” *Human Molecular Genetics*. 2021;30(18):1750-1761.

³⁹⁴ Betti M, Casalone E, Ferrante D, et al. “Germline mutations in DNA repair genes predispose asbestos-exposed patients to malignant pleural mesothelioma.” *Cancer Letters*. 2017;405:38-45.

³⁹⁵ This finding is also consistent with PTVs alone leading to development of mesothelioma.

prostate cancer, leukemia, papillary thyroid cancer, thyroid adenoma, lymphoma, and multiple myeloma.^{396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422}

- ³⁹⁶ Attanoos RL, Churg A, Galateau-Salle F, Gibbs AR, Roggli VL. "Malignant Mesothelioma and Its Non-Asbestos Causes." *Archives of Pathology & Laboratory Medicine*. 2018;142(6):753-760.
- ³⁹⁷ Betti M, Casalone E, Ferrante D, et al. "Inference on Germline BAP1 Mutations and Asbestos Exposure from the Analysis of Familial and Sporadic Mesothelioma in a High-Risk Area." *Genes, Chromosomes & Cancer*. 2015;54:51-62.
- ³⁹⁸ Carbone M, Yang H, Pass HI, Krausz T, Testa JR, et al. "BAP1 and cancer." *Nature Reviews Cancer*. 2013;13:153-159.
- ³⁹⁹ Cheung M, Talarchek J, Schindler K, Saraiva E, Penney PS, et al. "Further evidence for germline BAP1 mutations predisposing to melanoma and malignant mesothelioma." *Cancer Genetics*. 2013;206:206-210.
- ⁴⁰⁰ Cheung M, Kadariya Y, Talarchek J, Pei J, Ohar JA, et al. "Germline BAP1 mutation in a family with high incidence of multiple primary cancers and a potential gene-environment interaction." *Cancer Letters*. 2015;369:261-265.
- ⁴⁰¹ de la Fouchardière A, Cabaret O, Savin L, Combemale P, Schwartz H, et al. "Germline BAP1 mutations predispose also to multiple basal cell carcinomas." *Clinical Genetics*. 2015;88:273-277.
- ⁴⁰² Haugh AM, Njauw CN, Bubley JA, et al. "Genotypic and Phenotypic Features of BAP1 Cancer Syndrome: A Report of 8 New Families and Review of Cases in the Literature." *Journal of the American Medical Association Dermatology*. 2017;153(10):999-1006.
- ⁴⁰³ Kittaneh M, Berkelhammer C. "Detecting germline BAP1 mutations in patients with peritoneal mesothelioma: benefits to patient and family members." *Journal of Translational Medicine*. 2018;16(194):1-7.
- ⁴⁰⁴ Leblay N, Leprêtre F, Le Stang N, Gautier-Stein A, et al. "BAP1 Is Altered by Copy Number Loss, Mutation, and/or Loss of Protein Expression in More Than 70% of Malignant Peritoneal Mesotheliomas." *Journal of Thoracic Oncology*. 2017;12(4):724-733.
- ⁴⁰⁵ Lin M, Zhang L, Hildebrandt MAT, Huang M, Wu X, et al. "Common, germline genetic variations in the novel tumor suppressor BAP1 and risk of developing different types of cancer." *Oncotarget*. 2017;8(43):74936-74946.
- ⁴⁰⁶ McDonnell KJ, Gallanis GT, Heller KA, Melas M, Idos GE, et al. "A novel BAP1 mutation is associated with melanocytic neoplasms and thyroid cancer." *Cancer Genetics*. 2016;209:75-81.
- ⁴⁰⁷ Murali R, Wiesner T, and Scolyer RA. "Tumours associated with BAP1 mutations." *Pathology*. 2013;45(2):116-126.
- ⁴⁰⁸ Ohar JA, Cheung M, Talarchek J, Howard SE, Howard TD, et al. "Germline BAP1 Mutational Landscape of Asbestos-Exposed Malignant Mesothelioma Patients with Family History of Cancer." *Cancer Research*. 2016;76(2):206-215.
- ⁴⁰⁹ Popova T, Hebert L, Jacquemin V, Gad S, Caux-Moncoutier V, et al. "Germline BAP1 Mutations Predispose to Renal Cell Carcinomas." *The American Journal of Human Genetics*. 2013;92:974-980.
- ⁴¹⁰ Rai K, Pilarski R, Cebulla CM, and Abdel-Rahman MH. "Comprehensive review of BAP1 tumor predisposition syndrome with report of two new cases." *Clinical Genetics*. 2016;89:285-294.
- ⁴¹¹ Ribeiro C, Campelos S, Moura CS, Machado JC, Justino A, et al. "Well-differentiated papillary mesothelioma: clustering in a Portuguese family with a germline BAP1 mutation." *Annals of Oncology*. 2013;24:2147-2150.
- ⁴¹² Star P, Goodwin A, Kapoor R, Conway RM, Long GV, et al. "Germline BAP1-positive patients: the dilemmas of cancer surveillance and a proposed interdisciplinary consensus monitoring strategy." *European Journal of Cancer*. 2018;92:48-53.
- ⁴¹³ Wadt KAW, Aoude LG, Johansson P, Solinas A, Pritchard A, et al. "A recurrent germline BAP1 mutation and extension of the BAP1 tumor predispositions spectrum to include basal cell carcinoma." *Clinical Genetics*. 2015;88:267-272.
- ⁴¹⁴ Wang A, Papneja A, Hyrcza M, Al-Habeeb A, Ghazarian D. "Gene of the month: BAP1." *Journal of Clinical Pathology*. 2016;69(9):750-753.
- ⁴¹⁵ Sporn TA, Roggli VL. "Mesothelioma." Chapter 5 in *Pathology of Asbestos-Associated Diseases*, 2nd ed., edited by Victor L. Roggli, et al. (New York, NY: Springer-Verlag, 2004), 104-168.
- ⁴¹⁶ Pelnar PV. "Further Evidence of Nonasbestos-related Mesothelioma. A Review of the Literature." *Scandinavian Journal of Work and Environmental Health*. 1988;14:141-144.
- ⁴¹⁷ Peterson Jr. JT, Greenberg SD, Buffler PA. "Non-asbestos-related Malignant Mesothelioma. A Review." *Cancer*. 1984;54:951-960.

In patients with BAP-1 germline mutations, the prognosis may be much more favorable in mesothelioma than in those with sporadic mesothelioma. One study found a 7-fold increased long-term survival, with a median survival of 5 years with BAP-1 mutations vs. < 1 year in U.S. SEER data.^{423,424,425}

Peritoneal mesothelioma has been also reported in association with Lynch syndrome (LS).^{426,427,428,429,430,431,432,433,434} Lynch syndrome is an inherited cancer-prone syndrome and is characterized by a germline mutation in one of several DNA mismatch repair (MMR) genes (MSH2, MLH1, MSH6, PMS2, EPCAM) whose proteins function to maintain replications fidelity of DNA prior to mitosis.⁴³⁵ The most common cancers associated with Lynch syndrome are colon and uterine. In addition to the risk of colon and uterine cancer, those with Lynch

⁴¹⁸ Bott M, Brevet M, Taylor BS, et al. "The nuclear deubiquitinase BAP1 is commonly inactivated by somatic mutations and 3p21.1 losses in malignant pleural mesothelioma." *Nature Genetics*. 2011;43(7):668-672.

⁴¹⁹ Kadariya Y, Cheung M, Xu J, et al. "Bap1 Is a Bona Fide Tumor Suppressor: Genetic Evidence from Mouse Models Carrying Heterozygous Germline Bap1 Mutations." *Cancer Research*. 2016;76(9):2836-2844.

⁴²⁰ Testa JR, Cheung M, Pei J, et al. "Germline BAP1 mutations predispose to malignant mesothelioma." *Nature Genetics*. 2011;43:1022-1025.

⁴²¹ Carbone M, Harbour JW, Brugarolas, et al. "Biological Mechanisms and Clinical Significance of BAP1 Mutations in Human Cancer." *Cancer Discovery*. 2020;10:1103-1120.

⁴²² Carbone M, Arron ST, Beutler B, et al. "Tumour predisposition and cancer syndromes as models to study gene-environment interactions." *Nature Reviews Cancer*. 2020;20(9):533-549.

⁴²³ Baumann F, Buck BJ, Metcalf RV, et al. "The presence of asbestos in the natural environment is likely related to mesothelioma in young individuals and women from Southern Nevada." *Journal of Thoracic Oncology*. 2015;10(5):731-737.

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⁴²⁵ Panou V, Røe OD. "Inherited genetic mutations and polymorphisms in malignant mesothelioma: A comprehensive review." *International Journal of Molecular Sciences*. 2020;21(4327):1-17.

⁴²⁶ Shia J, Holck S, DePetrus G, et al. "Lynch syndrome-associated neoplasms: a discussion on histopathology and immunochemistry." *Familial Cancer*. 2013;12:241-260.

⁴²⁷ Karamurzin Y, Zeng Z, Stadler ZK, et al. "Unusual DNA mismatch repair-deficient in Lynch syndrome: a report of new cases and review of the literature." *Human Pathology*. 2012;43:1677-1687.

⁴²⁸ Carethers JM. "High predictability for identifying Lynch syndrome via microsatellite instability testing or immunohistochemistry in all Lynch-associated tumor types." *Translational Cancer Research*. 2019;8(Suppl 6):S559-S563.

⁴²⁹ Latham A, Srinivasan P, Kemel Y, et al. "Microsatellite Instability Is Associated With the Presence of Lynch Syndrome Pan-Cancer [published correction appears in J Clin Oncol. 2019 Apr 10;37(11):942]." *Journal of Clinical Oncology*. 2019;37(4):286-295.

⁴³⁰ Lu Y, Milchgrub S, Khatri G, Gopal P. "Metachronous Uterine Endometrioid Adenocarcinoma and Peritoneal Mesothelioma in Lynch Syndrome: A Case Report." *International Journal of Surgical Pathology*. 2017;25(3):253-257.

⁴³¹ Makiuchi S, Yoshida H, Ishikawa M, Kojima N, Kanai Y, Kato T. "Primary Peritoneal Low-grade Serous Carcinoma in a Patient With Lynch Syndrome: A Case Report." *International Journal of Gynecological Pathology*. 2019; 39:327-332.

⁴³² Malpica A, Euscher ED, Marques-Piubelli ML, et al. "Malignant Mesothelioma of the Peritoneum in Women: A Clinicopathologic Study of 164 Cases." *American Journal of Surgical Pathology*. 2021;45(1):45-58.

⁴³³ Rosenblum RE, Ang C, Suckiel SA, et al. "Lynch Syndrome-Associated Variants and Cancer Rates in an Ancestrally Diverse Biobank." *JCO Precision Oncology*. 2020;4:PO.20.00290.

⁴³⁴ Shih AR, Kradin RL. "Malignant mesothelioma in Lynch syndrome: A report of two cases and a review of the literature." *American Journal of Industrial Medicine*. 2019;62(5):448-452.

⁴³⁵ Carethers JM. "High predictability for identifying Lynch syndrome via microsatellite instability testing or immunohistochemistry in all Lynch-associated tumor types." *Translational Cancer Research*. 2019;8(Suppl 6):S559-S563.

syndrome have higher risks for cancers of the ovary, stomach, small intestine, hepatobiliary system, pancreas (including serous cystadenoma, acinar cell carcinoma, and well differentiated neuroendocrine tumor), renal pelvis and ureter, brain, and sebaceous glands. Other cancers reported in association with Lynch syndrome include adrenocortical, prostate, breast, cervix, larynx, hematologic malignancy, malignant fibrous histiocytoma, leiomyosarcoma of the extremity or uterus, liposarcoma, malignant melanoma, lung adenocarcinoma, and anaplastic carcinoma of the thyroid.^{436,437,438}

In a report by Karamurzin et al., a case of peritoneal mesothelioma was reported in a 56-year-old man with an MLH1 germline mutation, and whose tumor showed mutations in MLH1 and PMS2.⁴³⁹ Latham et al. reported on the prevalence of Lynch syndrome Pan-Cancer among more than 15,000 patients. 165 cases of mesothelioma were found, of whom 6 (1.7%) had Lynch syndrome.⁴⁴⁰ Lu and colleagues presented a case of a woman with Lynch syndrome who was diagnosed with peritoneal mesothelioma 10 months after being diagnosed with uterine endometrioid adenocarcinoma. The authors noted that the case raised the possibility that LS-associated primary peritoneal mesothelioma may present with more favorable histological features and carry a better prognosis than non-LS-associated peritoneal mesothelioma.⁴⁴¹ In the 2020 study by Rosenblum et al., a woman with LS was presented who had both pleural mesothelioma and endometrial cancer.⁴⁴² The paper by Shih and Kradin presented two cases from medicolegal litigation, both of whom had LS. One had peritoneal mesothelioma and one had well-differentiated papillary mesothelioma (WDPM) of the pleura.⁴⁴³

In support of a non-environmental role in causes of mesothelioma in the U.S., in a study published in 1994, the attributable risk of asbestos for both forms of mesothelioma in women combined was only 23%, meaning that 77% of mesotheliomas in women were not linked to asbestos exposure.⁴⁴⁴

⁴³⁶ Win AK, Lindor NM. "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis." *UpToDate*. Last updated: 20 November 2020.

⁴³⁷ Carethers JM. "High predictability for identifying Lynch syndrome via microsatellite instability testing or immunohistochemistry in all Lynch-associated tumor types." *Translational Cancer Research*. 2019;8(Suppl 6):S559-S563.

⁴³⁸ Karamurzin Y, Zeng Z, Stadler ZK, et al. "Unusual DNA mismatch repair-deficient tumors in Lynch syndrome: a report of new cases and review of the literature." *Human Pathology*. 2012;43(10):1677-1687.

⁴³⁹ Karamurzin Y, Zeng Z, Stadler ZK, et al. "Unusual DNA mismatch repair-deficient tumors in Lynch syndrome: a report of new cases and review of the literature." *Human Pathology*. 2012;43(10):1677-1687.

⁴⁴⁰ Latham A, Srinivasan P, Kemel Y, et al. "Microsatellite Instability Is Associated With the Presence of Lynch Syndrome Pan-Cancer [published correction appears in J Clin Oncol. 2019 Apr 10;37(11):942]." *Journal of Clinical Oncology*. 2019;37(4):286-295.

⁴⁴¹ Lu Y, Milchgrub S, Khatri G, Gopal P. "Metachronous Uterine Endometrioid Adenocarcinoma and Peritoneal Mesothelioma in Lynch Syndrome: A Case Report." *International Journal of Surgical Pathology*. 2017;25(3):253-257.

⁴⁴² Rosenblum RE, Ang C, Suckiel SA, et al. "Lynch Syndrome-Associated Variants and Cancer Rates in an Ancestrally Diverse Biobank." *JCO Precision Oncology*. 2020;4:PO.20.00290.

⁴⁴³ Shih AR, Kradin RL. "Malignant mesothelioma in Lynch syndrome: A report of two cases and a review of the literature." *American Journal of Industrial Medicine*. 2019;62(5):448-452.

⁴⁴⁴ Spirtas R, Heineman EF, Bernstein L, et al. "Malignant mesothelioma: attributable risk of asbestos exposure." *Occupational and Environmental Medicine*. 1994;51:804-811.

In some cases, called spontaneous cases, there are no known or suspected environmental causes, and these cases are considered to represent the background rate of mesothelioma. In women in the U.S., mesothelioma incidence rates have been fairly steady over several decades of observation, and, unlike the changing rates in men, they have not varied in relation to asbestos use patterns. These findings contrast with epidemic curves seen for diseases in women that followed an increase in tobacco use.⁴⁴⁵ Thus, the background, or spontaneous, rate can be estimated based on the relatively constant incidence rate in women, who infrequently have mesotheliomas caused by asbestos exposure.^{446,447,448,449,450,451,452,453,454,455}

Recent investigations have helped clinicians and scientists have a better understanding of how much cancer risk is from the environment, from heredity, and from errors in cell replication, informing multiple fields, including epidemiology. In a 2015 study, Tomasetti and Vogelstein demonstrated that the lifetime risk of many cancers is strongly correlated with the total number of divisions of the normal self-renewing cells. They estimated that about one-third of the variation in cancer risk was attributable to environmental factors or inherited predispositions, and that the remaining two-thirds were related to random mutations arising during replication in normal, non-cancerous stem cells.⁴⁵⁶ In a follow-up study, Tomasetti et al.⁴⁵⁷ pointed out that approximately three mutations occur every time a normal human stem cell divides, and they inferred that the reason for the previously reported correlation between stem cell divisions and cancer incidence was the driver gene mutations that randomly resulted from cell divisions. While their first study examined U.S. cancer rates, this newer study included data from 69 countries (4.8 billion people or 2/3 of the world population). As with the U.S. population alone, this worldwide study showed a very high correlation between the lifetime risk of multiple cancers and each tissue's lifetime number of stem cell divisions. The study further examined the

⁴⁴⁵ Thun M, Peto R, Boreham J, Lopez AD. "Stages of the cigarette epidemic on entering its second century." *Tobacco Control*. 2012;21:96-101.

⁴⁴⁶ Moore AJ, Parker RJ, Wiggins J. "Malignant Mesothelioma." *Orphanet Journal of Rare Diseases*. 2008;3(34):1-11.

⁴⁴⁷ Moolgavkar SH, Meza R, Turim J. "Pleural and peritoneal mesotheliomas in SEER: age effects and temporal trends, 1973-2005." *Cancer Causes Control*. 2009;20:935-944.

⁴⁴⁸ Moolgavkar SH, Chang ET, Mezei G, et al., "Epidemiology of Mesothelioma." Chapter 3 in *Asbestos and Mesothelioma*, Edited by Joseph R. Testa. (Philadelphia, PA: Springer, 2017). 43-72.

⁴⁴⁹ Tomasetti C, Vogelstein B. "Variation in Cancer Risk Among Tissues Can Be Explained by the Number of Stem Cell Divisions." *Science*. 2015;347(6217):78-81.

⁴⁵⁰ Tomasetti C, Li L, Vogelstein B. "Stem Cell Divisions, Somatic Mutations, Cancer Etiology, and Cancer Prevention." *Science*. 2017;355(6331):1330-1334.

⁴⁵¹ Price B, Ware A. "Mesothelioma Trends in the United States: An Update Based on Surveillance, Epidemiology, and End Results Program Data for 1973 through 2003." *American Journal of Epidemiology*. 2004;159(2):107-112.

⁴⁵² Price B, Ware A. "Time trend of mesothelioma incidence in the United States and projection of future cases: An update based on SEER data for 1973 through 2005." *Critical Reviews in Toxicology*. 2009;39(7):576-588.

⁴⁵³ Henley SJ, Larson TC, Wu M, et al. "Mesothelioma incidence in 50 states and the District of Columbia, United States, 2003-2008." *International Journal of Occupational and Environmental Health*. 2013;19(1):1-10.

⁴⁵⁴ Weill H, Hughes JM, Churg AM. "Changing Trends in US Mesothelioma Incidence." *Occupational and Environmental Medicine*. 2004;61(5):438-441.

⁴⁵⁵ Calthorpe L, Romero-Hernandez F, Miller P, et al. "Contemporary Trends in Malignant Peritoneal Mesothelioma: Incidence and Survival in the United States." *Cancers*. 2023;15(1):229.

⁴⁵⁶ Tomasetti C, Vogelstein B. "Variation in Cancer Risk Among Tissues Can Be Explained by the Number of Stem Cell Divisions." *Science*. 2015;347(6217):78-81.

⁴⁵⁷ Tomasetti C, Li L, Vogelstein B. "Stem Cell Divisions, Somatic Mutations, Cancer Etiology, and Cancer Prevention." *Science*. 2017;355(6331):1330-1334.

proportion of driver mutations that result from the environment, heredity, and replication errors. Using a database from the UK of cancers that “*have been studied in depth through sophisticated epidemiological investigations and are reported in the Cancer Research UK database,*” Tomasetti estimated that among the studied cancer types, 29% of driver gene mutations were caused by environmental factors and 5% were attributable to hereditary factors. About 66% of driver gene mutations were attributable to replication errors. The contribution of the environment varied, estimated as greater than 60% for cancers such as lung, esophagus, and skin and less than 15% for cancers such as prostate, brain, and breast. Regarding mesothelioma, driver gene mutations were estimated to be 65.7% attributed to the environment and 33.8% to replication errors. When examining women separately, the replication error contribution was 47% and the environment was 52.5%. Importantly, the contribution of the environment to cancer in the UK is markedly higher than that predicted in the U.S., as noted by Tomasetti, with Cancer Research UK estimating that 42% of cancers there are preventable, compared with only 21% in the U.S. estimated by the U.S. CDC. Such differences in the proportion of preventable cancers in different countries are related to different exposure circumstances, for example, in the UK (unlike the U.S.), women historically had heavy amphibole asbestos exposures in the workplace.^{458,459,460} In sum, it is clear that, in addition to environmental exposures and heredity, replication errors play an important role in contributing to rates of driver gene mutations and cancers, even in cancers with historical links to suspected environmental causes.

ENVIRONMENTAL ASBESTOS EXPOSURE AND MESOTHELIOMA.

In a 2016 study by Baumann and Carbone, the authors sought to understand the potential role of “*environmental exposure*” to asbestos to explain cases of mesothelioma that are not related to occupational exposure. In that study, they referenced that occupational cases of mesothelioma predominate in males and those of older age (average of 8th decade of life), while there are clusters of mesotheliomas where there is no occupational asbestos exposure, and the patients are younger and equally likely to be male or female. They also noted that because the assessment of exposure is made retrospectively, the exposure related to the environment is likely to be underestimated. The authors performed an analysis of mesothelioma mortality in the U.S. by state and by county and concluded that in areas with high proportions of younger cases (<55 years old) and more females that there were probable environmental exposures. This study provides a potential explanation for the risk of mesothelioma in non-occupationally exposed people, in addition to genetic risk factors and spontaneously formed tumors.⁴⁶¹

MESOTHELIOMA IN YOUNG PERSONS.

⁴⁵⁸ Peto J, Rake C, Gilham C, Hatch J. “Occupational, domestic and environmental mesothelioma risks in Britain. A case-control study.” *Health and Safety Executive (HSE), RR969 Research Report*. 2009.

⁴⁵⁹ Rake C, Gilham C, Hatch J, et al. “Occupational, domestic and environmental mesothelioma risks in the British population: a case-control study.” *British Journal of Cancer*. 2009;100:1175-1183.

⁴⁶⁰ Acheson ED, Gardner MJ, Pippard EC, et al. “Mortality of Two Groups of Women who Manufactured Gas Masks from Chrysotile and Crocidolite Asbestos: A 40-year Follow-Up.” *British Journal of Industrial Medicine*. 1982;39:344-348.

⁴⁶¹ Baumann F, Carbone M. “Environmental Risk of Mesothelioma in the United States: An Emerging Concern - Epidemiological Issues.” *Journal of Toxicology and Environmental Health, Part B*. 2016;19(5-6):231-249.

Mesothelioma is a rare tumor and is especially rare in children and young adults. There are reported cases of mesothelioma in patients without significant asbestos exposure, who are also of younger age. Less is known about mesothelioma in the young, but the known long latency for asbestos-induced disease makes it more likely that genetic predisposition and/or environmental exposure plays a role.⁴⁶² Germline mutations in *BRCA1* associated protein-1 (*BAP1*) may account for some of these cases.⁴⁶³ There are likely to be other genetic abnormalities linked to mesothelioma development in young people, as demonstrated in a study examining 25 cases of mesothelioma in adults younger than 40 years. That study found cases of *EWSR1* or *FUS-ATF1* gene fusions in people lacking a history of asbestos exposure, who also had retained expression of *BAP1*. Thus, there is emerging evidence for genetic contributions to the risk of mesothelioma, especially in those who are younger and who lack a history of asbestos exposure.⁴⁶⁴

TALC AND MESOTHELIOMA.

There is substantial evidence that talc is not a cause of mesothelioma. In 2010 IARC released a monograph that included their evaluation of talc not containing asbestiform fibers. The review by IARC included studies of cancer in humans with regard to cosmetic use of talc, occupational exposures, as well as talc in pleurodesis. The evaluation of the evidence led to an opinion that there is inadequate evidence in humans for the carcinogenicity of inhaled talc not containing asbestos or asbestiform fibers. IARC also noted that there is limited evidence for the carcinogenicity of perineal use of talc-based body powder. The overall evaluation resulted in perineal use as Group 2B (possibly carcinogenic) and inhaled talc as Group 3 (not classifiable as to its carcinogenicity). The working group considered the studies on talc miners and millers to be the “best source of evidence” but “no consistent pattern was seen.”⁴⁶⁵

Finley and colleagues performed an analysis in 2017 to determine if existing epidemiologic information supports the conclusion that cosmetic talc exposure can cause mesothelioma.⁴⁶⁶ The systematic review sought studies of miners and millers of cosmetic talc as well as follow-up of patients who had had talc pleurodesis performed. There were three longitudinal studies of miners and millers that provided 99,022 person-years of observation. There were no cases of mesothelioma in these studies.

⁴⁶² Thomas A, Chen Y, Yu T, Gill A, Prasad V. “Distinctive clinical characteristics of malignant mesothelioma in young patients.” *Oncotarget*. 2015;6(18):16766-16773.

⁴⁶³ Testa JR, Cheung M, Pei J, et al. “Germline *BAP1* Mutations Predispose to Malignant Mesothelioma.” *Nature Genetics*. 2011;43:1022-1025.

⁴⁶⁴ Desmeules P, Joubert P, Zhang L, et al. “A Subset of Malignant Mesotheliomas in Young Adults Are Associated With Recurrent *EWSR1/FUS-ATF1* Fusions.” *The American Journal of Surgical Pathology*. 2017;41(7):980-988.

⁴⁶⁵ International Agency for Research on Cancer (IARC). “Carbon Black, Titanium Dioxide, and Talc.” *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, World Health Organization. 2010:Volume 93.

⁴⁶⁶ Finley BL, Benson SM, Marsh GM. “Cosmetic Talc as a Risk Factor for Pleural Mesothelioma: A Weight of Evidence Evaluation of the Epidemiology.” *Inhalation Toxicology*. 2017;29(4):179-185.

Since the publication of the review by Finley et al., additional reports have been published about the Val Chisone and Norwegian miners and millers.^{467,468} These studies found no deaths from pleural cancer or mesothelioma. In an update to the Finley 2017 analysis, Marsh et al. reported analyses of the pooled 113,344 person-years in the cohorts and concluded that “*the epidemiological evidence from the cosmetic talc miner/miller cohort studies does not support the hypothesis that exposure to cosmetic talc is associated with the development of pleural cancer/mesothelioma.*”⁴⁶⁹

The pooled analysis of studies examined the potential long-term health effects of talc pleurodesis, with follow-up durations of 14 to 40 years. No cases of mesothelioma were found. There have been multiple publications regarding the safety of talc pleurodesis that show that talc instilled into the pleural space causes the intended inflammation and scarring, and that it has not been found to cause cancer, including mesothelioma.^{470,471,472,473,474,475} A recent article describing a review of published literature concluded that there is neither evidence for, nor reason to believe, that talc pleurodesis causes mesothelioma and that talc currently remains the gold standard agent for pleurodesis.⁴⁷⁶ It is important to note that the miners and millers were chronically exposed to high doses of cosmetic talc and the pleurodesis patients had several grams of talc applied directly to their pleural cavities.

One study by NIOSH examined Vermont miners and millers of talc.^{477,478} No asbestos was detected in the talc. No cases of mesothelioma were found in this study. Lung cancer mortality (not mesothelioma) was elevated in miners, but not millers “*despite probable higher dust exposures in mill operations.*” This finding by NIOSH investigators suggests that some factor(s)

⁴⁶⁷ Pira E, Coggiola M, Ciocan C, et al. “Mortality of Talc Miners and Millers from Val Chisone, Northern Italy.” *Journal of Occupational Environmental Medicine*. 2017;59(7):659-664.

⁴⁶⁸ Wergeland E, Gjertsen F, Vos L, Grimsrud TK. “Cause-specific mortality and cancer morbidity in 390 male workers exposed to high purity talc, a six-decade follow-up.” *American Journal of Industrial Medicine*. 2017;60(9):821-830.

⁴⁶⁹ Marsh GM, Ierardi AM, Benson SM, Finley BL. “Occupational exposures to cosmetic talc and risk of mesothelioma: an updated pooled cohort and statistical power analysis with consideration of latency period.” *Inhalation Toxicology*. 2019;31(6):213-223.

⁴⁷⁰ BTA, Chappell AG, Johnson A, et al. “A survey of the long-term effects of talc and kaolin pleurodesis.” Research Committee of the British Thoracic Association and the Medical Research Council Pneumoconiosis Unit. *British Journal of Diseases of the Chest*. 1979;73:285-288.

⁴⁷¹ Agarwal R, Paul AS, Aggarwal AN, et al. “A randomized controlled trial of the efficacy of cosmetic talc compared with iodopovidone for chemical pleurodesis.” *Respirology*. 2011;16:1064-1069.

⁴⁷² Kennedy L, Sahn SA. “Talc Pleurodesis for the Treatment of Pneumothorax and Pleural Effusion.” *Chest*. 1994;106(4):1215-1222.

⁴⁷³ Lange P, Mortenson J, Groth S. “Lung function 22-35 years after treatment of idiopathic spontaneous pneumothorax with talc poudrage or simple drainage.” *Thorax*. 1988;43:559-561.

⁴⁷⁴ Viskum K, Lange P, Mortenson J. “Long term Sequelae after Talc Pleurodesis for Spontaneous Pneumothorax.” *Pneumologie*. 1989;43:105-106.

⁴⁷⁵ Noppen M. “Talc Pleurodesis.” *UpToDate*. Last updated: 07 May 2018.

⁴⁷⁶ Baiu I, Yevudza E, Shrager JB. “Talc Pleurodesis: A Medical, Medicolegal, and Socioeconomic Review.” *The Annals of Thoracic Surgery*. 2020;109:1294-1301.

⁴⁷⁷ Selevan, SG, Dement, JM. “Mortality Patterns Among Miners and Millers of Non-Asbestiform Talc Preliminary Report.” In *Dusts and Disease*, edited by Lemen R, Dement JM. (Park Forest South, IL: Pathotox Publishers, Inc., 1979). 379-388.

⁴⁷⁸ Boundy MG, Gold K, Martin KP Jr, et al. “Occupational exposure to non-asbestiform talc in Vermont.” In: Lemen R, Dement JM, eds, *Dusts and Disease*, (Park Forest South, IL: Pathotox Publishers, Inc., 1979.) 365-378.

other than talc would possibly raise the risk of lung cancer, including differences in tobacco exposure (not assessed in the study).

In 2019 Fordyce et al.⁴⁷⁹ published findings from an updated and expanded cohort of Vermont talc miners and millers that was originally studied and reported by Selevan et al.⁴⁸⁰ While the original study examined workers employed between 1940 and 1969, the current updated cohort also includes workers employed from 1930 to 1940, as well as from 1970 to 1983. Mortality patterns were examined up through the end of 2012, rather than the original study's end of 1975. The updated study now included 427 workers with 17,170 person-years of observation. The Fordyce study showed that the cohort mortality rate was approximately 30% higher than the general U.S. population, while malignant neoplasms were not elevated. Significant elevations in mortality were found for non-malignant respiratory disease. As earlier versions of ICD coding did not include codes specific for mesothelioma, the authors employed a method of examining all ICD codes that could have potentially included cases of mesothelioma and employed a nosologist to examine the corresponding death certificates.⁴⁸¹ One case of mesothelioma was found by this method in a man whose death certificate stated that he had been exposed to asbestos. That worker had worked for less than five years in the talc industry, "*leaving open the possibility of exposure to asbestos in other occupations.*" The standardized mortality ratios (SMRs) for diseases captured by these studied SMRs were not significantly elevated, whether examined with or without lung cancer deaths. In subsequent correspondence, Fordyce et al. articulates that the single case of mesothelioma does not represent a significantly elevated rate and that the individual had asbestos exposure outside the Vermont talc mines and mills.⁴⁸² Since the Fordyce publications, updated analyses of several worldwide cohorts have concluded "*that it is very unlikely that the true value of the SMR for mesothelioma for the pooled cosmetic talc miner/miller cohorts is 2.0 or greater*" and that "*despite the recent finding of one case of mesothelioma in the Vermont cohort (a case unlikely related to talc exposure), we continue to conclude that the epidemiological evidence from the cosmetic talc miner/miller cohort studies does not support the hypothesis that cosmetic talc exposures are associated with an increased risk of pleural mesothelioma.*" In fact, the authors estimated that the probability that the true mesothelioma SMR is at or above 2.0 or 3.0 is 0.0096 and 0.0005, respectively.^{483,484}

⁴⁷⁹ Fordyce TA, Leonhard MJ, Mowat FS, Moolgavkar SH. "A 37-year Update on Mortality Patterns in an Expanded Cohort of Vermont Talc Miners and Millers." *Journal of Occupational Environmental Medicine*. 2019;61(11):916-923.

⁴⁸⁰ Selevan, SG, Dement, JM. "Mortality Patterns Among Miners and Millers of Non-Asbestiform Talc Preliminary Report." In *Dusts and Disease*, edited by Lemen R, Dement JM. (Park Forest South, IL: Pathotox Publishers, Inc., 1979). 379-388.

⁴⁸¹ Wojcik NC, Schnatter AR, Huebner WW. "Mesothelioma in Occupational Cohort Studies: Methodological Considerations." *Journal of Occupational and Environmental Medicine*. 2014;56(1):47-51.

⁴⁸² Fordyce TA, Leonhard MJ, Mowat FS, Moolgavkar SH. "Letter to the Editor: Response to Finkelstein Re: the Fordyce et al. Vermont Talc Miners and Millers Cohort Study Update." *Journal of Occupational and Environmental Medicine*. 2020;62(4):e172-e173.

⁴⁸³ Ierardi AM, Marsh GM. "Absence of mesothelioma risk maintained in an expanded international cohort of cosmetic talc miners and millers." *Inhalation Toxicology*. 2020;32(6):257-264.

⁴⁸⁴ Marsh GM, Ierardi AM. "Confidence interval function analysis to evaluate the risk of mesothelioma among an expanded international cohort of cosmetic talc miners and millers." *Regulatory Toxicology Pharmacology*. 2020;115:104696.

As the Vermont talc mines were found to be free of asbestos,^{485,486} if the talc worker with mesothelioma had had occupational asbestos exposure, it would have occurred in a different occupational setting. As made clear by Peto⁴⁸⁷ and Rake,⁴⁸⁸ when examining workers from low-risk settings, it is important to determine if those workers were also employed at other times in higher risk occupations. Otherwise, one can measure falsely elevated risks for mesothelioma that would be misattributed to the low-risk occupation. For example, in their case-control study, men in low-risk industrial jobs appeared to have an elevated risk of mesothelioma [OR(95% CI): 4.1 (2.6-6.4)], but there was no elevated risk after eliminating workers who had also had medium or high-risk industrial exposures [OR(95% CI): 1.1 (0.5-2.2)].^{489,490}

There are also studies from the Val Chisone Italian mine that fail to show any cases of mesothelioma in the miners and millers of talc, including the most recently updated analysis from 2021.^{491,492,493,494,495} Additional studies from talc mines in France, Norway, and Austria also failed to show any cases of mesothelioma among workers in those mines.^{496,497,498,499,500} With regard to France, in the study by Leophonte and Didier, the authors noted that the only French talc deposit being exploited was located in Luzenac in the South of France. The study noted that

⁴⁸⁵ Boundy MG, Gold K, Martin KP Jr, et al. "Occupational exposure to non-asbestiform talc in Vermont." In: Lemen R, Dement JM, eds, *Dusts and Disease*, (Park Forest South, IL: Pathotox Publishers, Inc., 1979.) 365-378.

⁴⁸⁶ Rossner A, Williams PR, Mellas-Hulett E, Rahman MA. "Analysis of Historical Worker Exposures to Respirable Dust from Talc Mining and Milling Operations in Vermont." *Annals of Work Exposures and Health*. 2020;64(4):416-429.

⁴⁸⁷ Peto J, Rake C, Gilham C, Hatch J. "Occupational, domestic and environmental mesothelioma risks in Britain. A case-control study." *Health and Safety Executive (HSE), RR969 Research Report*. 2009.

⁴⁸⁸ Rake C, Gilham C, Hatch J, et al. "Occupational, domestic and environmental mesothelioma risks in the British population: a case-control study." *British Journal of Cancer*. 2009;100:1175-1183.

⁴⁸⁹ Peto J, Rake C, Gilham C, Hatch J. "Occupational, domestic and environmental mesothelioma risks in Britain. A case-control study." *Health and Safety Executive (HSE), RR969 Research Report*. 2009.

⁴⁹⁰ Rake C, Gilham C, Hatch J, et al. "Occupational, domestic and environmental mesothelioma risks in the British population: a case-control study." *British Journal of Cancer*. 2009;100:1175-1183.

⁴⁹¹ Rubino GF, Scansetti G, Piolatto G, Romano CA. "Mortality Study of Talc Miners and Millers." *Journal of Occupational and Environmental Medicine*. 1976;18(3):186-193.

⁴⁹² Coggiola M, Bosio D, Pira E, et al. "An update of a mortality study of talc miners and millers in Italy." *American Journal of Industrial Medicine*. 2003;44(1):63-69.

⁴⁹³ Pira E, Coggiola M, Ciocan C, et al. "Mortality of Talc Miners and Millers From Val Chisone, Northern Italy." *Journal of Occupational and Environmental Medicine*. 2017;59(7):659-664.

⁴⁹⁴ Rubino GF, Scansetti G, Piolatto G, Gay G. "Mortality and Morbidity Among Talc Miners and Millers in Italy." In: Lemen R, Dement JM, Eds, *Dusts and Disease*. (Park Forest South, IL: Pathotox Publishers, Inc., 1979). 357-363.

⁴⁹⁵ Ciocan C, Pira E, Coggiola M, et al. "Mortality in the cohort of talc miners and millers from Val Chisone, Northern Italy: 74 years of follow-up." *Environmental Research*. 2022;203:111865.

⁴⁹⁶ Leophonte P, Didier A. "French Talc Pneumoconiosis." *Health Related Effects of Phyllosilicates*. NATO ASI Series, Springer, Berlin, Heidelberg. 1990;21:203-209.

⁴⁹⁷ Wergeland E, Gjertsen F, Vos L, Grimsrud TK. "Cause-specific mortality and cancer morbidity in 390 male workers exposed to high purity talc, a six-decade follow-up." *American Journal of Industrial Medicine*. 2017;60(9):821-830.

⁴⁹⁸ Wergeland E, Andersen A, Berheim A. "Morbidity and mortality in talc-exposed workers." *American Journal of Industrial Medicine*. 1990;17(4):505-513.

⁴⁹⁹ Wild P, Leodolter K, Refregier M, Schmidt H, Bourgard E. "Effects of talc dust on respiratory health: results of a longitudinal survey of 378 French and Austrian talc workers." *Occupational and Environmental Medicine*. 2008;65(4):261-267.

⁵⁰⁰ Wild P. "A cohort mortality and nested case-control study of French and Austrian talc workers." *Occupational and Environmental Medicine*. 2002;59(2):98-105.

the talc does not contain asbestos. The authors reported that pneumoconiosis was frequent among talc workers and related to dust overexposure, but there were no carcinogenic risks and no mesothelioma.⁵⁰¹ In Wild 2002, cohorts of talc workers were followed in France and Austria. The French cohort included 1,070 people contributing 28,849 person-years of observation. Mortality from pneumoconiosis was significantly elevated, while mesothelioma risk was not (0 cases observed).⁵⁰²

Airborne Dust Concentrations in Talc Mines and Mills.

Respirable dust particles are those that are small enough to penetrate deeply into the lungs. There are several studies that have assessed concentrations of respirable dust in talc mines and mills.⁵⁰³ For example, samples from three Vermont mines evaluated from 1975 to 1976 showed mean exposures to respirable dust from 0.5 to 5.1 mg/m³ in the mines and 0.5 to 2.9 mg/m³ in the mills, with concentrations generally higher in the mills than the mines.^{504,505}

Another study examined respirable dust from Vermont mining and milling operations in the time period from 1976 to 2003. By MSHA measures, the average concentration was 1.8 mg/m³ and by company data 0.81 mg/m³. The study showed that a number of job categories exceeded the ACGIH TLV of 2 mg/m³ and the OSHA and MSHA PEL of approximately 3 mg/m³.⁵⁰⁶ In the studies of Italian talc miners and millers, high dust concentrations were documented at different time periods with steady reductions over a period of decades. Respirable dust was estimated at 100 to 1000 MPPCF before 1955 and less than 10 MPPCF between 1960 and 1975 (some conversions from MPPCF to mg/m³ include for talc 1 MPPCF=0.1 mg/m³ and for nuisance dust 1 MMPCF=0.33 mg/m³).^{507,508}

In a paper from 2003, more recent estimates were that mean respirable dust was 1.1 mg/m³, ranging from 0.5 to 2.5 mg/m³.^{509,510} In the 2007 to 2014 time range, average respirable dust

⁵⁰¹ Leophonte P, Didier A. "French Talc Pneumoconiosis." *Health Related Effects of Phyllosilicates*. 1990:203-209.

⁵⁰² Wild P. "A cohort mortality and nested case-control study of French and Austrian talc workers." *Occupational and Environmental Medicine*. 2002;59(2):98-105.

⁵⁰³ International Agency for Research on Cancer (IARC). "Carbon Black, Titanium Dioxide, and Talc." *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. World Health Organization. 2010:Volume 93.

⁵⁰⁴ International Agency for Research on Cancer (IARC). "Carbon Black, Titanium Dioxide, and Talc." *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. World Health Organization. 2010:Volume 93.

⁵⁰⁵ Boundy MG, Gold K, Martin KP Jr, et al. "Occupational exposure to non-asbestiform talc in Vermont." In: Lemen R, Dement JM, eds, *Dusts and Disease*, (Park Forest South, IL: Pathotox Publishers, Inc., 1979.) 365-378.

⁵⁰⁶ Rossner A, Williams PR, Mellas-Hulett E, Rahman MA. "Analysis of Historical Worker Exposures to Respirable Dust from Talc Mining and Milling Operations in Vermont." *Annals of Work Exposures and Health*. 2020;64(4):416-429.

⁵⁰⁷ National Institute for Occupational Safety and Health (NIOSH). "Talc (containing no asbestos and less than 1% quartz)." *NIOSH Pocket Guide to Chemical Hazards*. 2018.

⁵⁰⁸ Occupational Safety and Health Administration (OSHA). "Table Z-3 Mineral Dusts." *United States Department of Labor*. Available at: <https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.1000TABLEZ3>. 2016.

⁵⁰⁹ Rubino GF, Scansetti G, Piolatto G, Romano CA. "Mortality Study of Talc Miners and Millers." *Journal of Occupational and Environmental Medicine*. 1976;18(3):186-193.

⁵¹⁰ Coggiola M, Bosio D, Pira E, et al. "An update of a mortality study of talc miners and millers in Italy." *American Journal of Industrial Medicine*. 2003;44(1):63-69.

varied with job and year but ranged from more than 0.2 to 1.6 mg/m³.⁵¹¹ In the study by Wild et al. of workers in a French talc-producing factory, respirable dust from 1986 to 1991 was measured as a mean of 0.5 to 15 mg/m³, with estimates in the past up to 60 mg/m³.⁵¹² In the study of workers at a talc mine in northern Norway, investigators reported that personal air samples varied with job category and workplace with mean concentrations of 0.9 to 97 mg/m³ and peak exposures during drilling of 319 mg/m³.⁵¹³

To put these very high dust concentrations into a more familiar context, one can consider the allowable dust concentrations in U.S. outdoor air. Airborne dust is also called particulate matter (PM), and PM comes from numerous natural and man-made sources.^{514,515} For outdoor, or ambient air, the U.S. EPA specifies allowable limits to the respirable dust concentration, defined as PM_{2.5}, or particles that are less than or equal to 2.5 microns. The annual allowable concentration is 12 microns/m³ (equivalent to 0.012 mg/m³).⁵¹⁶ Notably, this maximum allowable limit is orders of magnitude less than the average exposure values of the studied talc miners and millers. Some perspective is apparent from visually observing days with dust concentrations of 0.032 and 0.004 mg/m³, where the higher concentration is a hazy day and the lower one is clear.^{517,518}

⁵¹¹ Pira E, Coggiola M, Ciocan C, et al. "Mortality of Talc Miners and Millers From Val Chisone, Northern Italy." *Journal of Occupational and Environmental Medicine*. 2017;59(7):659-664.

⁵¹² Wild P, Refregier, Auburtin G, et al. "Survey of the Respiratory health of the workers of a talc producing factory." *Occupational and Environmental Medicine*. 1995;52:470-477.

⁵¹³ Wergeland E, Andersen A, Berheim A. "Morbidity and mortality in talc-exposed workers." *American Journal of Industrial Medicine*. 1990;17(4):505-513.

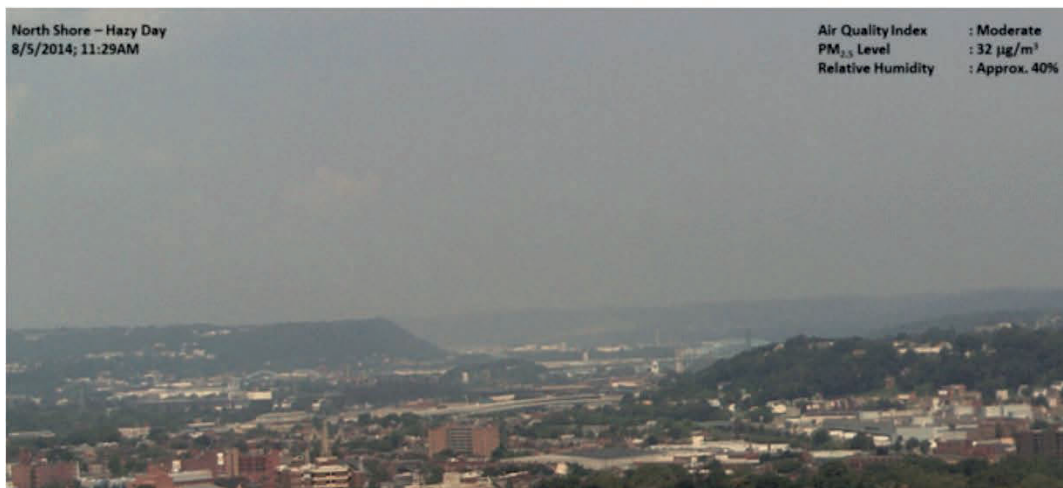
⁵¹⁴ American Thoracic Society (ATS). "Health Effects of Outdoor Air Pollution." *American Journal of Respiratory and Critical Care Medicine*. 1996;153:3-50.

⁵¹⁵ James J, Clark C, Rice J. "Exploring the differences between ambient air data and emissions inventory." *Crustal Matter*. 18 March 2009.

⁵¹⁶ Environmental Protection Agency (EPA). "Revised Air Quality Standards for Particle Pollution and Updates to the Air Quality Index (AQI)." *The National Ambient Air Quality Standards for Particle Pollution*. 2012.

⁵¹⁷ AirNow.gov. AirNow Visibility Cameras. Available at: <https://www.airnow.gov/index.cfm?action=airnow.webcams>. Accessed: 06 September 2019.

⁵¹⁸ Breathe Project. Breathe Cam. Available at: <https://breatheproject.org/learn/breathe-cam/>. Published 2019. Accessed: 06 September 2019 (via AirNow.gov).



Images of exact same location taken at 11:29AM on two separate dates – on a clear day (7/4) details on the horizon are clearly visible; on a hazy day (8/5) fine particle (PM_{2.5}) concentration is high and white haze covers the hillside.

Summary Report of Gregory B. Diette, M.D., M.H.S.

In the famous London Fog air pollution event, PM concentrations were estimated to be approximately 3 mg/m^3 , and about 12,000 London residents died as a result. Images from the time period visibly show the appearance of dust of this magnitude.^{519,520}



Nelson's column during the 1952 smog disaster. (Source: geograph.org.uk/N T Stobbs)

⁵¹⁹ Bell ML, Davis DL. "Reassessment of the Lethal London Fog of 1952: Novel Indicators of Acute and Chronic Consequences of Acute Exposure to Air Pollution." *Environmental Health Perspectives*. 2001;109(3):389-394.

⁵²⁰ Davis DL, Bell ML, Fletcher T. "A Look back at the London Smog of 1952 and the Half Century Since." *Perspectives Guest Editorials*. 2002;110(12):A734-A735.

Summary Report of Gregory B. Diette, M.D., M.H.S.



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⁵²¹ Associated Newspapers/Rex Fea/Rex Features. Guardian. Available at: <https://www.theguardian.com/environment/gallery/2012/dec/05/60-years-great-smog-london-in-pictures>. Published: 05 December 2012. Accessed: 25 October 2019.

In contrast to heavy industrial exposures to talc in miners and millers, Burns et al.⁵²³ demonstrated that potential exposures to asbestos in talc to consumers of talcum powder are quite low and below general population background airborne cumulative lifetime exposure. The authors used published and unpublished measurement data associated with talcum powder products and applied the “*EPA’s current nonoccupational asbestos regulatory risk assessment methods and other important benchmarks.*” For four different use scenarios, authors estimated cumulative exposure potential ranging from 0.0000021 to 0.0096 f/cc-yr, which resulted in risk estimates that were within or below EPA’s acceptable target risk levels. The authors concluded that their findings were consistent with the original EPA findings from 1985 and that exposure and corresponding health risk in this range were orders of magnitude below upper-bound estimates of cumulative asbestos exposure and risk at ambient levels, which have not been associated with increased incidence of asbestos-related disease. Lifetime ambient cumulative exposure to asbestos in the U.S. population ranges from approximately 0.002-0.4 f/cc-yr over a 70-year lifetime.^{524,525}

EXPERT REPORTS & OPINIONS.

R. Mark Bailey, PG.^{526,527,528,529,530,531,532,533,534,535,536}

Mr. Bailey is a geologist and mineralogist who performed transmission electron microscopy analysis on samples of Avon and Johnson & Johnson talcum powder products. The results of his studies showed tremolite, chrysotile, anthophyllite, serpentine, and actinolite fibers in some of the samples that he tested. One sample that Mr. Bailey tested was found to contain numerous

⁵²² PA. “Arsenal goalkeeper Jack Kelsey peers into the fog, searching for the elusive ball.” *Guardian*. Available at: <https://www.theguardian.com/environment/gallery/2012/dec/05/60-years-great-smog-london-in-pictures>. Published: 05 December 2012. Accessed: 25 October 2019.

⁵²³ Burns AM, Barlow CA, Banducci AM, et al. “Potential Airborne Asbestos Exposure and Risk Associated with the Historical Use of Cosmetic Talcum Powder Products.” *Risk Analysis*. 2019;39(10):2272-2294.

⁵²⁴ Burns AM, Barlow CA, Banducci AM, et al. “Potential Airborne Asbestos Exposure and Risk Associated with the Historical Use of Cosmetic Talcum Powder Products.” *Risk Analysis*. 2019;39(10):2272-2294.

⁵²⁵ Agency for Toxic Substances and Disease Registry (ATSDR). “Toxicological Profile for Asbestos: Potential for Human Exposure.” *U.S. Department of Health and Human Services, Public Health Service* (2001).

⁵²⁶ Expert Report of R. Mark Bailey, PG, Laboratory Test Results for Avon Pavi Elle Perfumed Talc, Floral Fantasy, and 2 Odesseys, dated 27 December 2021.

⁵²⁷ Expert Report of R. Mark Bailey, PG, Montana Talc Report on behalf of Avon, dated 12 June 2015.

⁵²⁸ Expert Report of R. Mark Bailey, PG, Analysis of Avon Cotillion, dated 17 December 2019.

⁵²⁹ Expert Report of R. Mark Bailey, PG, Laboratory Test Results for Avon Soft Musk and Topaze Perfumed Talc, dated 13 October 2021.

⁵³⁰ Expert Report of R. Mark Bailey, PG, Laboratory Test Results for Avon To a Wild Rose, dated 19 January 2024.

⁵³¹ Murphy, North Carolina Talc Chart of Documents for Mark Bailey, PG, dated 20 August 2021.

⁵³² Expert Report of R. Mark Bailey, PG, on Asbestos in Talc Products from the Fontane Mine, Val Germanasca, Italy for Avon, dated 12 June 2020.

⁵³³ Expert Report of R. Mark Bailey, PG, on Asbestos in Talc Products from the Hammondsville Mine, Vermont, USA for Avon, 16 November 2020.

⁵³⁴ Affidavit of R. Mark Bailey, on behalf of Johnson & Johnson, dated 30 October 2023, with exhibits 1 through 16.

⁵³⁵ Expert Report of R. Mark Bailey, PG, Transmission Electron Microscopy Analytical Test Report of Johnson & Johnson Baby Powder, dated 06 May 2021.

⁵³⁶ Expert Report of R. Mark Bailey, PG, Transmission Electron Microscopy Analytical results for 3 talc archive batch samples on behalf of Johnson & Johnson, dated 08 September 2021.

richterite, and several aluminum-containing fibers which were designated as richterite/winchite, amphibole asbestos fibers; fibrous talc was also observed.

Mr. Bailey determined that commercial talc deposits from southwestern Montana, including the Regal and Treasure mines owned by Barretts Minerals, were produced by hydrothermal alteration of dolomitic rocks creating large asbestos-free talc deposits.

Mr. Bailey examined talc from the Fontane mine. He reports that the talc material derived from the Fontane mine is consistently contaminated with tremolite/actinolite minerals, ranging in form from prismatic to asbestiform and that chrysotile asbestos is also found in the mine at times as well.

Mr. Bailey examined talc from the Hammondsville Mine in Vermont. He reports that the talc from the Hammondsville mine consistently contained trace amounts of fibrous tremolite/actinolite, and for any given bottle, within the limits of statistical uncertainty, there exists an extremely high scientific likelihood that the amphibole minerals tremolite/actinolite and/or anthophyllite will be present when the talc came from the Hammondsville talc mine.

Mr. Bailey holds the opinion that Johnson & Johnson talc products containing talc sourced from the Fontane mine in Italy and the Vermont mines identified above consistently contained asbestos.

William E. Longo, PhD.^{537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560}

Dr. Longo provided opinions about various talcum powders and performed analyses of various talcum powders from Avon, Estée Lauder, and Johnson & Johnson.

Dr. Longo has the opinion that the application of talcum powder found in a number of samples of Avon talcum powder products would cause significant exposure, over background, to chrysotile asbestos to individuals who used Avon brand talcum powder products for their intended purpose. For two samples of Avon talcum powder products Dr. Longo has the opinion that when children were exposed to these types of Avon's talcum powder products, they would have had a significant exposure to chrysotile, over background levels. For one sample of Avon talcum powder, Dr. Longo has the opinion that the application of the talcum powder found in this

⁵³⁷ MAS Talcum Powder Analysis, Jeannine Henderson- Avon Wild Country, prepared by William E. Longo, PhD, CEO dated 25 October 2023.

⁵³⁸ MAS Report on Avon Talcum Powder Analysis with both Automated FESEM and ATEM, dated 12 March 2019.

⁵³⁹ MAS Analysis Report of Chinese Talc Research Samples, prepared by William E. Longo, PhD, CEO dated 16 September 2020.

⁵⁴⁰ MAS Analysis Report of Avon Occur Perfumed Talc, prepared by William E. Longo, PhD, dated 18 August 2021.

⁵⁴¹ MAS Talcum Powder Analysis of Avon and Clinique Containers, prepared by William E. Longo, PhD, dated 05 September 2021.

⁵⁴² MAS Talcum Powder Analysis of Montana Micro-Talc 1745 Retain Samples, prepared by William E. Longo, PhD, CEO dated 10 June 2022.

⁵⁴³ MAS Talcum Powder Analysis of Avon Splits, prepared by William E. Longo, PhD, CEO dated 01 June 2022.

⁵⁴⁴ MAS Talcum Powder Analysis of Historical Avon Splits: Wild Rose 1965, Cotillion 1961, & Persian Wood 1958, prepared by William E. Longo, PhD, CEO dated 01 June 2022.

⁵⁴⁵ MAS Pfizer Treasure Mine Talc Analysis, prepared by William E. Longo, PhD, CEO dated 01 June 2022.

⁵⁴⁶ MAS Talc Ore Samples Collected from the Eclipse Mine in Death Valley: Analyzed for Amphibole Asbestos by Transmission Electron Microscopy, prepared by William E. Longo, PhD, CEO dated 12 June 2022.

⁵⁴⁷ MAS Talcum Powder Analysis of Rita Chapman Avon Powder Containers, prepared by William E. Longo, PhD, CEO dated 01 June 2022.

⁵⁴⁸ MAS Supplemental Report Avon Talcum Powder Container Analysis for Asbestos, prepared by William E. Longo, PhD, CEO dated 30 September 2022.

⁵⁴⁹ MAS Talcum Powder Analysis of Avon Powder Products, Project M71387 & M71587, prepared by William E. Longo, PhD, CEO dated 15 November 2022.

⁵⁵⁰ MAS Talcum Powder Analysis of Avon Powder Products, Project M71560 & M71562, prepared by William E. Longo, PhD, CEO dated 15 November 2022.

⁵⁵¹ MAS Analysis Report of Avon Products, prepared by William E. Longo, PhD, dated 15 November 2022.

⁵⁵² MAS Supplemental Report Talcum Powder Analysis of Avon Powder Products, Project M71560 & M71562, prepared by William E. Longo, PhD, CEO dated 19 November 2022.

⁵⁵³ MAS Talcum Powder Analysis of Avon Somewhere Powder, prepared by William E. Longo, PhD, CEO dated 20 September 2023.

⁵⁵⁴ MAS Talcum Powder Analysis of Avon Split, prepared by William E. Longo, PhD, CEO dated 21 September 2023.

⁵⁵⁵ MAS Avon Talcum Powder Analysis, prepared by William E. Longo, PhD, CEO dated 21 September 2023.

⁵⁵⁶ MAS Talcum Powder Analysis of Solomon, Beth – Talc Splits, prepared by William E. Longo, PhD, CEO dated 16 February 2024.

⁵⁵⁷ MAS Analysis Report of Avon Unforgettable Perfumed Talc, prepared by William E. Longo, PhD, dated 21 April 2017.

⁵⁵⁸ MAS Expert Analysis Report of Estee Lauder Products by William E. Longo, PhD, CEO, dated 16 December 2022.

⁵⁵⁹ MAS 4th Supplemental MDL Report, Analysis of Non-Historical J&J's Talcum Powder Consumer Product Containers and J&J Chinese Historical Talc Retain Samples, by William E. Longo, PhD, CEO, dated 29 April 2024.

⁵⁶⁰ Declaration of William Longo, PhD, dated 21 September 2021.

sample would cause significant exposure, over background, to chrysotile and tremolite asbestos to individuals who used Avon brand talcum powder products for their intended purpose.

Dr. Longo states that his opinion of the analytical results of 11 Guiguang Zhzhu, China Mine Source samples, is that the application of talcum powder from the Guiguang Zhzhu, China talc source, would have caused significant exposures over background to both chrysotile asbestos and fibrous talc.

Dr. Longo has the opinion that when individuals use cosmetic talc products that contain talcum powder from Pfizer's Montana Treasure Mine, it will cause these individuals to have significant exposure over background to chrysotile asbestos and potentially tremolite. It is his opinion that products that use talc sourced from the Eclipse talc mine would cause that product to contain significant amounts of amphibole asbestos and that individuals who use consumer products that contain talc from the Eclipse mine, where the product generates airborne dust during its use, will cause that individual to be exposed to significant levels of amphibole asbestos over background levels. He identified richterite asbestos and tremolite asbestos.

Dr. Longo has the opinion that the application of the talcum powder found in Estée Lauder body powder containers will cause significant exposure, over background, to tremolite asbestos and/or chrysotile to individuals, who used Estée Lauder brand talcum body powder products for their intended purpose, that used the same talcum powder mine source as the 12 Estée Lauder containers that were found to be positive for asbestos.

According to Dr. Longo, his analysis demonstrated that both the Italian and the Vermont mines that J&J sourced their talcum powder from contained significant amounts of amphibole asbestos (tremolite & anthophyllite/cummingtonite). Additionally, 15 talc ore samples sourced from their Vermont mine, were found to contain tremolite asbestos. He concludes that for the three talc mine sources that supplied J&J talcum powder for their two body powder products sold in the United States, Dr. Longo's company, MAS, has analyzed 96 containers of J&J talcum powder, He states that these products had detectable concentrations of asbestos in 82% of the containers and the 26 historical talc ore samples that MAS has analyzed, sourced from the Vermont and Chinese talc mines, found 73% positive for asbestos.

Dr. Longo reports that he tested Johnson & Johnson products that encompass the eras of all three sources for Johnson & Johnson talc products offered for sale in the United States (Italy, Vermont, China) as well as talc offered for sale in Asia, Australia, Argentina, and the United Kingdom. According to Dr. Longo, testing has shown regulated asbestos in containers sourced from each of these mines.

William E. Longo, PhD and Mark W. Rigler, PhD.⁵⁶¹

Dr. Longo and Dr. Rigler used three principal analytical methods for the analysis of the one 1987 Avon Night Magic cosmetic talc sample was polarized light microscopy (PLM), analytical transmission electron microscopy (ATEM) and field emission scanning electron microscopy (FE-SEM). Drs. Longo and Rigler conclude that The Blount/PLM and ISO 22262-2 ATEM method demonstrated that actinolite asbestos was in the Avon Night Magic Container. The weight concentration of the actinolite asbestos was found to be <0.1% by Blount PLM and 4240

⁵⁶¹ MAS Analysis of Avon Night Magic Talcum Powder, prepared by William E. Longo, PhD, and Mark W. Rigler, PhD, dated January 2019.

fiber/bundles by the 150- 22262-2 ATEM method and Cyprus's Olympic talc product, from the Beaverhead mine contains amphibole asbestos.

William E. Longo, PhD, Mark W. Rigler, PhD, and William B. Egeland, MS, PG.⁵⁶²

Dr. Longo, Dr. Rigler, and Mr. Egeland performed a study using both the NIOSH 7400 PCM method and the NIOSH 7402 TEM method to determine if any detectable amphibole asbestos fibers from a sample of Johnson's Baby Powder were released into the breathing zone of the investigator and immediate surrounding area in the exposure characterization lab. Dr. Longo, Dr. Rigler, and Mr. Egeland conclude that the four personal air samples that were collected in the breathing zone of the investigator showed an average mean tremolite asbestos fiber exposure of 2.57 f/cc and an average mean fibrous talc exposure of 1.95 f/cc. They explain that their results show that an individual, who uses asbestos-containing Johnson's talcum powder, can have a significant exposure to airborne amphibole fibers as shown in this study, and the magnitude of the asbestos fiber exposure levels will depend on the concentration level of the naturally occurring asbestos in the Johnson's Baby Powder product. They further state that their study showed that there was significant exposure to asbestiform talc fibers from the application of the Johnson's Baby Powder during the study.

William E. Longo, PhD, William B. Egeland, MS, PG, and Martin Bennett.^{563,564}

Dr. Longo, Mr. Egeland, and Mr. Bennett performed a work practice study regarding Johnson's Baby Powder Application to baby during diaper change. Personal samples detected asbestos fibers.

Steven P. Compton, PhD.^{565,566,567,568,569,570,571}

Dr. Compton investigated several talc/mineral samples for asbestos. According to Dr. Compton, amphibole fibers were detected in eleven of the thirteen Italian Talc samples. He states that aside from the talc itself, the primary fibrous contaminants in the sample set are anthophyllite and

⁵⁶² MAS Supplemental #2 Expert Report on Below the Waist Application of Johnson & Johnson Baby Powder by William E. Longo, PhD, Mark W. Rigler, PhD, and William B. Egeland, MS, PG, dated January 2018.

⁵⁶³ MAS Expert Report Rev #1 on Talcum Powder Application to Baby and Diaper Change II: A Hygiene Study by William E. Longo, PhD, William B. Egeland, MS, PG, and Martin Bennett, dated 28 June 2019.

⁵⁶⁴ MAS Expert Report on Johnson's Baby Powder Application to Baby and Diaper Change: A Hygiene Study Supplemental by William E. Longo, PhD, William B. Egeland, MS, PG, and Martin Bennett, dated May 2020.

⁵⁶⁵ Expert Report of Steven P. Compton, PhD, Investigation of Italian Talc Samples for Asbestos, dated 01 August 2017.

⁵⁶⁶ Expert Report of Steven P. Compton, PhD, Investigation of Vermont Talc Samples for Asbestos, dated 23 April 2018.

⁵⁶⁷ Expert Report of Steven P. Compton, PhD, Investigation of Montana Talc (American International Industries Microtalc 1745) for Asbestos, dated 15 March 2019.

⁵⁶⁸ Expert Report of Steven P. Compton, PhD, Examination of Avon Talcum Powder for Asbestos Gail Welch Case, dated 29 May 2020.

⁵⁶⁹ Expert Report of Steven P. Compton, PhD, Examination of 907 Talc Powder for Asbestos, dated 26 January 2024.

⁵⁷⁰ Expert Report of Steven P. Compton, PhD, Examination of Vintage Avon Bunny Fluffpuff Talc in Rabbit-shaped Puff container for Asbestos, dated 19 May 2023.

⁵⁷¹ Expert Report of Steven P. Compton, PhD, Examination of Vintage Avon Unforgettable Talc in Shaker Container for Asbestos, dated 19 May 2023.

tremolite/actinolite, and the asbestos content of samples found to contain amphibole and chrysotile fibers range from approximately 1.7 to 660 million fibers per gram.

Dr. Compton also reported that amphibole fibers were detected in ten of the fifteen samples analyzed from the Argonaut Vermont mine, and aside from the talc itself, the primary fibrous contaminants in the sample set are anthophyllite and, in one sample, tremolite/actinolite. According to Dr. Compton, the asbestos content of samples found to contain amphibole fibers range from approximately 1.2 to 2,600 million fibers per gram.

Dr. Compton reported that asbestos fibers were detected by TEM in 6 of 53 Microtalc samples sourced from Montana that were collected from 2002 to 2017. According to Dr. Compton, aside from the talc itself, fibrous particles detected in the sample set include chrysotile, tremolite, and anthophyllite (including anthophyllite/gedrite), and for samples in which asbestos was detected, the asbestos content ranged from approximately 3.6 to 9.5 million fibers per gram.

Dr. Compton's investigation of a sample of Avon talcum powder showed that it contains platy talc as well as fibrous talc and chrysotile asbestos fibers/bundles. Dr. Compton investigated another sample of Avon talcum powder and determined that the analyzed sample of talcum powder product contains platy talc as well as elongate mineral fibers of talc and the amphibole minerals tremolite/actinolite, and the amphibole asbestos concentration can be expressed as less than 79.6 million fibers per gram of powder (the upper 95% confidence interval). Dr. Compton investigated a third sample of Avon talcum powder which he determined contains platy talc as well as elongate mineral fibers of talc, tremolite asbestos, and sodium calcium amphibole fibers. The tremolite asbestos concentration, based on the detection of fibrous tremolite structures via TEM, is approximately 1.95 billion fibers per gram.

Dr. Compton analyzed a sample of 907 talc powder which he determined contains platy and fibrous talc in addition to calcium-rich mineral fibers, like tremolite and possible diopside.

Alan M. Segrave, PG.⁵⁷²

Mr. Segrave provided opinions as a geologist and microscopist on the occurrence of asbestos in proximity to talc deposits, specifically, the talc deposits of Val Chisone, Italy; Murphy, North Carolina; southwest Montana; Alpine, Alabama; southern Vermont, southeast California, Canada, Brazil, and Guangxi, China. Mr. Segrave states that talc sourced by Avon did not contain asbestos. Mr. Segrave also states that there is no evidence that Vi-Jon talc used in the manufacture of Equate body powder, 2003-2016 was contaminated with asbestos and it is unknown what talc was specifically used in the manufacture of Equate body powder, 2003-2016 product Mr. Perry allegedly used or was in proximity to its use. Mr. Segrave also states that talc sourced by IMI Fabi in products Mr. Perry used did not contain asbestos.

It is his opinion that the testing program performed by mining companies and independent laboratories relied upon by distributors (such as IMI Fabi and Vi-Jon) as well as manufacturers was a proactive, forward-thinking program to characterize asbestos in talc. Mr. Segrave's conclusions include that it is unlikely Mr. Perry would have been exposed to asbestos from the use of Avon Bird of Paradise, Cotillion, Skin So Soft, Soft Musk, Timeless, Topaze, Men's Musk, Deep Woods, and Spicy Talc body powders, and talc supplied by Vi-Jon or IMI Fabi. Mr.

⁵⁷² Expert Report of Alan M. Segrave, PG, dated 17 June 2024.

Segrave's opinion is that there is no evidence that Mr. Perry used or was in proximity to talc that was contaminated with asbestos, and which allegedly may have been used the above products.

Matthew S. Sanchez, PhD.^{573,574}

Dr. Sanchez provided opinions about the alleged contamination of asbestos in talc products manufactured by Estée Lauder using talc from a variety of sources. His opinion is that the Estée Lauder talcum-based products at issue in this case do not contain asbestos.

Dr. Sanchez also provided an analysis in this case and concluded that Johnson & Johnson talcum powder and talc from the source mines were and is free of asbestos. Dr. Sanchez's opinions are based on his review, analysis, and interpretation of the available analytical testing data on Johnson & Johnson talcum powder and talc from its three source mines: Val Germanesca Italy, southern Vermont USA, and Guangxi China.

Paul A. Nony, PhD, CIH, CSP.⁵⁷⁵

Dr. Nony calculated a hypothetical estimate, 0.000014 f/cc-yr, of Mr. Perry's cumulative exposure to asbestos as a result of his mother's described use of talc products manufactured by Estée Lauder. Comparatively, Dr. Nony figured Mr. Perry's estimated cumulative exposure from breathing asbestos present in ambient air through his date of disease diagnosis. He concluded that any hypothetical cumulative exposure to asbestos experienced by Mr. Perry associated with his mother's use of ELC talcum powder products was approximately 379 times less than his cumulative exposure resulting from ambient exposures in the environment.

Dr. Nony concluded the hypothetical exposure experienced by Mr. Perry did not present any significant risk toward his development of pleural mesothelioma. Any hypothetical exposure from ELC talcum powders would be substantially less than Mr. Perry's ambient exposure and of no significance towards his risk of developing disease.

Christy A. Barlow, PhD.⁵⁷⁶

Dr. Barlow reviewed case materials pertaining to Mr. Perry. Her opinion is that the chemistry, geometry, and biological reactivity of talc particles in cosmetic talcs are different from asbestos fibers. Likewise, cleavage fragments are not reactive and are distinctly and functionally different from asbestos fibers. Dr. Barlow has the opinion that increased rates in the development of mesothelioma associated with exposure to cosmetic talc have not been reported in the numerous experimental and epidemiological studies that have evaluated the carcinogenic potential of cosmetic talc. Dr. Barlow determined that based on the available evidence, Mr. Perry was unlikely to have been exposed to any measurable asbestos from his use of Johnson & Johnson talcum powders. Dr. Barlow further stated that using a worst-case assumption that trace asbestos could theoretically have been found in the Johnson & Johnson talcum powders, any associated asbestos exposure potential would have been well within (or below) the corresponding cumulative background or ambient levels of asbestos found in the air in the U.S., and below the cumulative asbestos exposure potential associated with working at the current OSHA PEL for asbestos over 45 years. Dr. Barlow estimated that the cumulative, worst-case asbestos fiber

⁵⁷³ Expert Report of Matthew S. Sanchez, on behalf of Johnson & Johnson, dated 06 June 2024.

⁵⁷⁴ Expert Report of Matthew S. Sanchez, on behalf of Estée Lauder, dated 06 June 2024.

⁵⁷⁵ Expert Report of Paul A. Nony, PhD, CIH, CSP, on behalf of Estée Lauder, dated 26 June 2024.

⁵⁷⁶ Expert Report of Christy A. Barlow, PhD, on behalf of Johnson & Johnson, dated 18 June 2024.

exposure estimate for Mr. Perry's consumer use of Johnson & Johnson talcum powders ranged from 0.0002 to 0.04 f/cc-yr.

Dr. Barlow also opined that Mr. Perry was unlikely to have been exposed to any measurable asbestos from his use of cosmetic talcum powder distributed by IMI Fabi LLC and IMI Fabi (Diana) LLC. Dr. Barlow further stated that using a worst-case assumption that trace asbestos could theoretically have been found in the cosmetic talcum powder distributed by IMI Fabi LLC and IMI Fabi (Diana) LLC, any associated asbestos exposure potential would have been well within (or below) the corresponding cumulative background or ambient levels of asbestos found in the air in the U.S., and below the cumulative asbestos exposure potential associated with working at the current OSHA PEL for asbestos over 45 years. Dr. Barlow estimated that the cumulative, worst-case asbestos fiber exposure estimate for Mr. Perry's consumer use of cosmetic talcum powder distributed by IMI Fabi LLC and IMI Fabi (Diana) LLC beginning in 2001, ranged from 0.0001 to 0.03 f/cc-yr.

Jennifer S. Pierce, MS, PhD.⁵⁷⁷

Dr. Pierce reviewed legal and medical materials pertaining to Mr. Perry, as well as materials pertaining to Avon in this matter. Dr. Pierce has the opinion that the weight of the evidence does not support that cosmetic talcum powders contain asbestiform minerals. She states that it is generally accepted that the development of asbestos-related cancer is not associated with exposure to talc that does not contain asbestiform minerals; however, if one were to assume that a cosmetic talcum powder product contained asbestiform minerals, the asbestos-related disease risk associated with that product is dependent on the chemical and physical properties of the asbestiform minerals present. She explained that even if one assumed that Avon cosmetic talcum powder products contained a trace level of asbestiform minerals, Mr. Perry's hypothetical exposure would have been well below the cumulative asbestos exposure that is permitted by the federal government (in the occupational setting), below that associated with breathing ambient air, and far too low to increase his risk of asbestos-related disease. Dr. Pierce's opinion is that Mr. Perry's disease may be unrelated to asbestos, and if asbestos-related, any hypothetical asbestos exposure that Mr. Perry may have experienced as a result of Avon products would not have increased his risk of developing mesothelioma.

Dr. Pierce calculated Mr. Perry's total hypothetical bystander exposure to asbestos from his mother's puff applications of Avon talcum powder to a range from 0.000099 f/cc-years to 0.0023 f/cc-years. She calculated Mr. Perry's total hypothetical bystander exposure to asbestos from his mother's personal shaker applications of Avon talcum powders (assuming a trace level of contamination) to a range from 0.00017 f/cc-years to 0.0049 f/cc-years. Dr. Pierce calculated that, overall, assuming a trace level of contamination in every Avon talcum powder product that Mr. Perry's mother ever applied in his vicinity, Mr. Perry's total hypothetical exposure to asbestos fibers resulting from this product would range from 0.00027 f/cc-years to 0.0072 f/cc-years. Dr. Pierce explains that the cumulative exposure over a working lifetime at the current Permissible Exposure Limit is 4.5 f/cc-years (i.e., 0.1 f/cc x 45 years), and Mr. Perry's hypothetical cumulative exposure to asbestos associated with Avon products is between approximately 625- and 16,729-fold below the cumulative occupational exposure that is currently acceptable in the United States. According to Dr. Pierce, Mr. Perry's total hypothetical

⁵⁷⁷ Expert Report of Jennifer S. Pierce, MS, PhD, in the matter of Michael Perry regarding Avon, Inc., dated 19 June 2024.

cumulative exposure to asbestos associated with Avon products throughout his lifetime is lower than the cumulative exposure associated with a lifetime of breathing ambient air; lower than the NOAELs for chrysotile, amosite, and crocidolite; and lower than the NOAEL for anthophyllite and tremolite asbestos.

Jennifer Sahmel, PhD, CIH, CSP, FAIHA.⁵⁷⁸

Dr. Sahmel evaluated case-specific materials pertaining to Mr. Perry. Dr. Sahmel indicated that her understanding that the relevant period during which Walmart-brand Equate baby powder could have been manufactured by Vi-Jon was between January of 2003 and August of 2016. Her opinion is that Mr. Perry was unlikely to have had the opportunity for exposure to any measurable asbestos from consumer use of powder products associated with Vi-Jon. According to Dr. Sahmel, even using an upper bound assumption that trace asbestos could theoretically have been found in Equate baby powder to which Mr. Perry was exposed between 2003 and 2016, according to any available data, any associated asbestos exposure potential would have been well within the corresponding cumulative background or ambient levels of asbestos found in the air in the U.S. However, Dr. Sahmel notes that Mr. Perry's actual cumulative asbestos exposure potential associated with the use of Equate baby powder potentially associated with Vi-Jon could have been below the limit of detection, if not zero. This is well below the cumulative asbestos exposure associated with a working lifetime at the current OSHA PEL for asbestos. She further notes that exposures to asbestos to the general U.S. population across a wide range of measured background airborne fiber concentrations have not been shown to be associated with a statistically significant increased risk of asbestos-related disease, including mesothelioma. Mr. Perry's total estimated cumulative lifetime exposure from Equate baby powder potentially associated with Vi-Jon could have been 0 f/cc-year or up to as much as a theoretical upper bound of 0.0086 f/cc-year, which is well below the range of reported lifetime ambient asbestos exposures in the U.S, if not below the limit of detection. Dr. Sahmel also states that any asbestos exposure potential associated with the use of cosmetic talc under more realistic scenarios is likely to be even further within or below the range of general cumulative ambient exposure, and orders of magnitude below the current OSHA PEL for asbestos.

ASSESSMENT.

The allegation in this case is that Mr. Perry has pleural mesothelioma that was caused by cosmetic talc believed to also contain asbestos. I have assumed that the diagnosis of pleural mesothelioma is correct. Based on the materials available in this case, Mr. Perry does not have conditions such as diffuse pleural thickening or bilateral calcified pleural plaques which, if present, could be compatible with prior asbestos exposure. He does not have asbestosis.

In particular, I assessed the evidence in this case that asbestos as a potential contaminant of cosmetic talc produced and/or distributed by Johnson & Johnson, Avon, Vi-Jon, Estée Lauder, Gold Bond, Ammens IMI-Fabi, LLC, IMI Fabi (USA), LLC, and/or IMI-Fabi (Diana) could have been responsible for causing pleural mesothelioma in Mr. Perry. In this case, there is no objective evidence available that shows that Mr. Perry had any asbestos exposure from his alleged use of cosmetic talc produced and/or distributed by Johnson & Johnson, Avon, Vi-Jon,

⁵⁷⁸ Expert Report of Jennifer Sahmel, PhD, CIH, CSP, FAIHA, on behalf of Vi-Jon, dated 20 June 2024.

Estée Lauder, Gold Bond, Ammens, IMI-Fabi, LLC, and/or IMI-Fabi (Diana) . There is no epidemiological evidence that the use of cosmetic talc produced and/or distributed by Johnson & Johnson, Avon, Vi-Jon, Estée Lauder, Gold Bond, Ammens, IMI-Fabi, LLC, IMI Fabi (USA), LLC, and/or IMI-Fabi (Diana) causes mesothelioma.

According to the testimony of Mr. Perry, his exposure to Johnson's Baby Powder was from his own personal use, his application to his husband, his husband's application to himself in his proximity, his mother's application to herself in his proximity, and his mother's application directly to him. Mr. Perry's exposure to Avon cosmetic talcum powder products was from playing with his father's container of powder and from being in proximity to his mother while she applied powder to herself. Mr. Perry's exposure to Vi-Jon cosmetic talcum powder products was from his application to himself and his application to his husband, and his husband's application to himself in Mr. Perry's proximity. Mr. Perry's exposure to Estée Lauder cosmetic talcum powder products was from being in proximity to his mother while she applied powder to herself. Mr. Perry's exposure to Gold Bond and Ammens cosmetic talcum powder products was from his own personal use and from applying powder to his shoes. Mr. Perry's exposure to cosmetic talc allegedly produced by IMI-Fabi, LLC, IMI Fabi (USA), LLC, and/or IMI Fabi (Diana), LLC was from talcum powder products since 2001.

Mr. Perry likely had no asbestos exposure from cosmetic talc produced and/or distributed by Johnson & Johnson, Avon, Vi-Jon, Estée Lauder, IMI-Fabi, LLC, and/or IMI-Fabi (Diana), but even worst-case estimated exposures would have been to a dose too low to elevate his risk for mesothelioma. It is not plausible that his alleged exposures from cosmetic talc produced and/or distributed by Johnson & Johnson, Avon, Vi-Jon, Estée Lauder, Gold Bond, Ammens, IMI-Fabi, LLC, IMI Fabi (USA), LLC, and/or IMI-Fabi (Diana) caused his mesothelioma.

I have not seen evidence in this case of any significant exogenous exposure (including asbestos) that would raise his risk of developing pleural mesothelioma, though I cannot rule out a contribution from his claimed occupational exposures. If Mr. Perry did not have significant exogenous exposure from commercial amphibole asbestos, it is most likely that his mesothelioma developed spontaneously or was naturally occurring.

It is possible that Mr. Perry had an inherited genetic risk factor for cancer especially given his young age, and personal and family history of malignancies. However, there is no germline testing result available to confirm that.

CONCLUSIONS.

Based on the review of case materials and medical and scientific literature relevant to this case, I express my opinions with a reasonable degree of medical certainty, including that:

- Mr. Perry was diagnosed with pleural mesothelioma in July 2023.
- Talc is not a carcinogen. Talc does not cause mesothelioma.

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- There is no objective evidence that Mr. Perry had any exposure to asbestos from cosmetic talc produced and/or distributed by Johnson & Johnson, Avon, Vi-Jon, Estée Lauder, Gold Bond, Ammens, IMI-Fabi, LLC, IMI Fabi (USA), LLC, and/or IMI-Fabi (Diana).
- Based on the available medical and scientific literature, it is not plausible that asbestos as a potential contaminant of cosmetic talc produced and/or distributed by Johnson & Johnson, Avon, Vi-Jon, Estée Lauder, Gold Bond, Ammens, IMI-Fabi, LLC, IMI Fabi (USA), LLC, and/or IMI-Fabi (Diana), could have caused Mr. Perry to develop pleural mesothelioma.
- I cannot rule out a contribution to his mesothelioma from his reported asbestos exposures at work. If Mr. Perry did not have significant asbestos exposure from his work or any other source, it is most likely that his mesothelioma developed spontaneously or was naturally occurring.
- It is possible that Mr. Perry has a hereditary risk for developing cancer. However, there is no available germline testing to confirm whether or not he has a hereditary risk factor.

This report is based on the information available to me at this time. Should additional information become available, I reserve the right to determine the impact, if any, of the new information on my opinions and conclusions, to revise my opinions and conclusions if necessary, and to rebut the opinions of any other experts that formulate an opinion in this matter.

Respectfully submitted,



Gregory B. Diette, M.D., M.H.S.

APPENDIX A: CASE MATERIALS AND OTHER DOCUMENTS RECEIVED.

Legal Documents/Materials:

- Summons and Complaint
- First Amended Summons and Complaint
- Second Amended Summons and Complaint
- Plaintiff's Responses to Defendants' Master Set of Interrogatories and Requests for Production (Ex. 2)
- Plaintiffs' Responses to Defendants' Standard Interrogatories
- Plaintiffs' First Supplemental Responses to Defendants' Standard Interrogatories
- Plaintiffs' First Supplemental Responses to Defendants' Master Set of Interrogatories and Requests for Production (Ex. 2)

Depositions:

- Video-recorded Deposition of Michael L. Perry, Volume I, taken 10 October 2023, *with* Exhibits 1 through 14.
- Video-recorded Deposition of Michael L. Perry, Volume II, taken 11 October 2023, *with* Exhibits A through D.
- Video-recorded Deposition of Michael L. Perry, Volume III, taken 12 October 2023.
- Video-recorded Deposition of Michael L. Perry, Volume IV, taken 13 October 2023.

Expert Reports & Materials:

- Expert Report of Matthew S. Sanchez, on behalf of Johnson & Johnson, dated 06 June 2024.
- Expert Report of Matthew S. Sanchez, on behalf of Estée Lauder, dated 06 June 2024.
- Expert Report of Alan M. Segrave, PG, dated 17 June 2024.
- Expert Report of Christy A. Barlow, PhD, on behalf of Johnson & Johnson, dated 18 June 2024.
- Expert Report of R. Mark Bailey, PG, Laboratory Test Results for Avon Pavi Elle Perfumed Talc, Floral Fantasy, and 2 Odesseys, dated 27 December 2021.
- Expert Report of R. Mark Bailey, PG, Montana Talc Report on behalf of Avon, dated 12 June 2015.
- Expert Report of R. Mark Bailey, PG, Analysis of Avon Cotillion, dated 17 December 2019.
- Expert Report of R. Mark Bailey, PG, Laboratory Test Results for Avon Soft Musk and Topaze Perfumed Talc, dated 13 October 2021.
- Expert Report of R. Mark Bailey, PG, Laboratory Test Results for Avon To a Wild Rose, dated 19 January 2024.

- Murphy, North Carolina Talc Chart of Documents for Mark Bailey, PG, dated 20 August 2021.
- Expert Report of R. Mark Bailey, PG, on Asbestos in Talc Products from the Fontane Mine, Val Germanasca, Italy for Avon, dated 12 June 2020.
- Expert Report of R. Mark Bailey, PG, on Asbestos in Talc Products from the Hammondsville Mine, Vermont, USA for Avon, 16 November 2020.
- MAS Talcum Powder Analysis, Jeannine Henderson- Avon Wild Country, prepared by William E. Longo, PhD, CEO dated 25 October 2023.
- MAS Analysis of Avon Night Magic Talcum Powder, prepared by William E. Longo, PhD, and Mark W. Rigler, PhD, dated January 2019.
- MAS Report on Avon Talcum Powder Analysis with both Automated FESEM and ATEM, dated 12 March 2019.
- MAS Analysis Report of Chinese Talc Research Samples, prepared by William E. Longo, PhD, CEO dated 16 September 2020.
- MAS Analysis Report of Avon Occur Perfumed Talc, prepared by William E. Longo, PhD, dated 18 August 2021.
- MAS Talcum Powder Analysis of Avon and Clinique Containers, prepared by William E. Longo, PhD, dated 05 September 2021.
- MAS Talcum Powder Analysis of Montana Micro-Talc 1745 Retain Samples, prepared by William E. Longo, PhD, CEO dated 10 June 2022.
- MAS Talcum Powder Analysis of Avon Splits, prepared by William E. Longo, PhD, CEO dated 01 June 2022.
- MAS Talcum Powder Analysis of Historical Avon Splits: Wild Rose 1965, Cotillion 1961, & Persian Wood 1958, prepared by William E. Longo, PhD, CEO dated 01 June 2022.
- MAS Pfizer Treasure Mine Talc Analysis, prepared by William E. Longo, PhD, CEO dated 01 June 2022.
- MAS Talc Ore Samples Collected from the Eclipse Mine in Death Valley: Analyzed for Amphibole Asbestos by Transmission Electron Microscopy, prepared by William E. Longo, PhD, CEO dated 12 June 2022.
- MAS Talcum Powder Analysis of Rita Chapman Avon Powder Containers, prepared by William E. Longo, PhD, CEO dated 01 June 2022.
- MAS Supplemental Report Avon Talcum Powder Container Analysis for Asbestos, prepared by William E. Longo, PhD, CEO dated 30 September 2022.
- MAS Talcum Powder Analysis of Avon Powder Products, Project M71387 & M71587, prepared by William E. Longo, PhD, CEO dated 15 November 2022.
- MAS Talcum Powder Analysis of Avon Powder Products, Project M71560 & M71562, prepared by William E. Longo, PhD, CEO dated 15 November 2022.

- MAS Analysis Report of Avon Products, prepared by William E. Longo, PhD, dated 15 November 2022.
- MAS Supplemental Report Talcum Powder Analysis of Avon Powder Products, Project M71560 & M71562, prepared by William E. Longo, PhD, CEO dated 19 November 2022.
- MAS Talcum Powder Analysis of Avon Somewhere Powder, prepared by William E. Longo, PhD, CEO dated 20 September 2023.
- MAS Talcum Powder Analysis of Avon Split, prepared by William E. Longo, PhD, CEO dated 21 September 2023.
- MAS Avon Talcum Powder Analysis, prepared by William E. Longo, PhD, CEO dated 21 September 2023.
- MAS Talcum Powder Analysis of Solomon, Beth – Talc Splits, prepared by William E. Longo, PhD, CEO dated 16 February 2024.
- MAS Analysis Report of Avon Unforgettable Perfumed Talc, prepared by William E. Longo, PhD, dated 21 April 2017.
- Expert Report of Steven P. Compton, PhD, Investigation of Italian Talc Samples for Asbestos, dated 01 August 2017.
- Expert Report of Steven P. Compton, PhD, Investigation of Vermont Talc Samples for Asbestos, dated 23 April 2018.
- Expert Report of Steven P. Compton, PhD, Investigation of Montana Talc (American International Industries Microtalc 1745) for Asbestos, dated 15 March 2019.
- Expert Report of Steven P. Compton, PhD, Examination of Avon Talcum Powder for Asbestos Gail Welch Case, dated 29 May 2020.
- Expert Report of Steven P. Compton, PhD, Examination of 907 Talc Powder for Asbestos, dated 26 January 2024.
- Expert Report of Steven P. Compton, PhD, Examination of Vintage Avon Bunny Fluffpuff Talc in Rabbit-shaped Puff container for Asbestos, dated 19 May 2023.
- Expert Report of Steven P. Compton, PhD, Examination of Vintage Avon Unforgettable Talc in Shaker Container for Asbestos, dated 19 May 2023.
- Expert Report of Jennifer S. Pierce, MS, PhD, in the matter of Michael Perry regarding Avon, Inc., dated 19 June 2024.
- Affidavit of R. Mark Bailey, on behalf of Johnson & Johnson, dated 30 October 2023, with exhibits 1 through 16.
- MAS Expert Analysis Report of Estee Lauder Products by William E. Longo, PhD, CEO, dated 16 December 2022.
- Expert Report of R. Mark Bailey, PG, Transmission Electron Microscopy Analytical Test Report of Johnson & Johnson Baby Powder, dated 06 May 2021.

- Expert Report of R. Mark Bailey, PG, Transmission Electron Microscopy Analytical results for 3 talc archive batch samples on behalf of Johnson & Johnson, dated 08 September 2021.
- MAS 4th Supplemental MDL Report, Analysis of Non-Historical J&J's Talcum Powder Consumer Product Containers and J&J Chinese Historical Talc Retain Samples, by William E. Longo, PhD, CEO, dated 29 April 2024.
- MAS Supplemental #2 Expert Report on Below the Waist Application of Johnson & Johnson Baby Powder by William E. Longo, PhD, Mark W. Rigler, PhD, and William B. Egeland, MS, PG, dated January 2018.
- MAS Expert Report Rev #1 on Talcum Powder Application to Baby and Diaper Change II: A Hygiene Study by William E. Longo, PhD, William B. Egeland, MS, PG, and Martin Bennett, dated 28 June 2019.
- MAS Expert Report on Johnson's Baby Powder Application to Baby and Diaper Change: A Hygiene Study Supplemental by William E. Longo, PhD, William B. Egeland, MS, PG, and Martin Bennett, dated May 2020.
- Declaration of William Longo, PhD, dated 21 September 2021.
- Expert Report of Jennifer Sahmel, PhD, CIH, CSP, FAIHA, on behalf of Vi-Jon, dated 20 June 2024.
- Expert Report of Paul A. Nony, PhD, CIH, CSP, on behalf of Estée Lauder, dated 26 June 2024, *with* References.

Other:

- Social Security Records of Michael Perry, 1979 through 2000.
- Social Security Records of Michael Perry, 1987 through 2023.
- Work History Affidavit.

Medical Documents/Materials:

- PERRY - MUSC 2.8.23-11.17.23
- PERRY - RSFP ROPER 2022-2023
- PERRY ROPER 5.19.17-7.1.23
- SC-PERRY MUSC radiology link
- Perry, Michael - Roper St. Francis (Dx Pathology Report 07.05.23) PERRY_SC_000014-000015 (3065538)
- Admission to Medical University of South Carolina dated 080823
- Admission to Palmetto Digestive Health Specialists dated 062623
- Cardiac testing
- Office notes of Charleston Oncology

- Office notes of Medical University of South Carolina (reverse chron)
- Office notes of Roper St. Francis Physician Partners
- Pathology reports
- Radiology reports
- Perry, Michael - Dr. Brian M. Lingerfelt (Medical 07.07.23)
- Perry, Michael - Edgepark Medical Supplies (Medical 07.07.23)
- Perry, Michael - Medical University of South Carolina (Pathology)
- Perry, Michael - MUSC (Pathology Report 08.18.23)
- Perry, Michael - MUSC Medical University of S. Carolina (Medical 07.08.23 - 08.18.23 Vol 1)
- Perry, Michael - MUSC Medical University of S. Carolina (Medical 07.08.23 - 08.18.23 Vol 2)
- Perry, Michael - MUSC Medical University of S. Carolina (Medical 07.08.23 - 08.18.23 Vol 3)
- Perry, Michael - MUSC Medical University of S. Carolina (Medical 08.22.23 - 12.26.23 Vol 1 - UC)
- Perry, Michael - MUSC Medical University of S. Carolina (Medical 08.22.23 - 12.26.23 Vol 2)
- Perry, Michael - MUSC Medical University of South Carolina (Medical Affidavit 07.08.23 - 08.18.23)
- Perry, Michael - Palmetto Digestive Disease Endoscopy Center (Medical 06.19.17 - 06.26.23)
- Perry, Michael - Palmetto Digestive Disease Endoscopy Center (Medical Affidavit 06.19.17 - 06.26.23)
- Perry, Michael - Pulmonology at MUSC Health Hollings Cancer Center (Medical 07.15.23 - 07.24.23)
- Perry, Michael - Pulmonology at MUSC Health Hollings Cancer Center (Medical Affidavit 07.15.23 - 07.24.23)
- Perry, Michael - Roper Hospital (Medical 03.01.21 - 06.30.23)
- Perry, Michael - Roper Hospital (Pathology)
- Perry, Michael - Roper St. Francis (Dx Pathology Report 07.05.23)
- Perry, Michael - Roper St. Francis Healthcare (Medical Vol 1 01.11.21 - 07.12.23)
- Perry, Michael - Roper St. Francis Healthcare (Medical Vol 2 01.11.21 - 07.12.23)
- Perry, Michael - Roper St. Francis Healthcare (Medical

- Admission to Medical University of South Carolina dated 07.24.23.
- Admission to Palmetto Digestive Health Specialists dated 04.10.19.
- Admission to Palmetto Digestive Health Specialists dated 06.05.23.
- Admission to Palmetto Digestive Health Specialists dated 06.19.17.
- Admission to Palmetto Digestive Health Specialists dated 07.12.17.
- Admission to Palmetto Digestive Health Specialists dated 08.09.17.
- Admission to Palmetto Endoscopy Center dated 01.20.14.
- Admission to Roper Hospital dated 06.30.23.
- Office notes of Medical University of South Carolina.
- Pathology reports; 02.25.10.
- Radiology reports; 06.11.17.
- Office notes of Medical University of South Carolina (reverse chron).
- Radiology reports; 12.05.23.
- Radiology Materials – Refer to **APPENDIX C** for list of studies received on disc format
 - 03 disc(s) on 10 May 2024 from Medical University of South Carolina.
 - 01 disc(s) on 04 June 2024 from Medical University of South Carolina.

APPENDIX B: LITERATURE CONSIDERED, REPORTS REVIEWED AND OTHER RELIANCE MATERIALS.

Abelmann A, Glynn ME, Pierce JS, et al. "Historical ambient airborne asbestos concentrations in the United States – an analysis of published and unpublished literature (1960s-2000s)." *Inhalation Toxicology*. 2015;27(14):754-766.

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APPENDIX C: RADIOLOGY STUDIES, AS RECEIVED ON COMPACT DISCS.**Medical University of South Carolina, 20 studies:**

- NM Pulmonary Ventilation Perfusion VQ, Accession Number: 21078587, dated 07/14/2023.
- MRI Brain W WO Contrast, Accession Number: 21076525, dated 07/17/2023.
- MRI Chest W WO Contrast, Accession Number: 21076526, dated 07/17/2023.
- PET CT Skull Base to Midthigh, Accession Number: 21053965, dated 07/18/2023.
- XR Chest 1 View Portable, Accession Number: 21178471, dated 08/08/2023.
- XR Chest 1 View Portable, Accession Number: 21178636, dated 08/08/2023.
- XR Chest AP Portable, Accession Number: 21178863, dated 08/09/2023.
- XR Chest AP Portable, Accession Number: 21182695, dated 08/10/2023.
- XR Chest AP Portable, Accession Number: 21187659, dated 08/11/2023.
- XR Chest AP Portable, Accession Number: 21192101, dated 08/12/2023.
- XR Chest 2 Views, Accession Number: 21194509, dated 08/13/2023.
- XR Chest 2 Views, Accession Number: 21195964, dated 08/14/2023.
- XR Chest 2 Views, Accession Number 21200519, dated 08/15/2023.
- XR Chest 2 Views, Accession Number: 21201843, dated 08/15/2023.
- XR Chest PA and Lateral, Accession Number: 21266398, dated 09/01/2023.
- CT Chest W Contrast, Accession Number: 21290447, dated 09/29/2023.
- CT Chest W Contrast, Accession Number: 21567301, dated 12/05/2023.
- RAD ONC PLANNING, Accession Number: 21555596, dated 01/02/2024.
- RAD ONC PLANNING, Accession Number: 21873777, dated 01/31/2024
- CT Chest W Contrast, Accession number: 21822953, dated 04/29/2024.

EXHIBIT 2

Gregory B. Diette, M.D., M.H.S.

02 July 2024

Gregory B. Diette, M.D., M.H.S.
8805 Columbia 100 Parkway
Suite 101
Columbia, Maryland 21045

Ms. Lucy Willson, Esq.
Willcox & Savage, PC
440 Monticello Avenue, Suite 2200
Norfolk, Virginia 23510

RE: Perry, Michael v. Johnson & Johnson, *et al.*

Dear Ms. Willson,

This supplemental report has been prepared at your request as an updated summary of my opinions regarding claims that M. Michael Perry developed pleural mesothelioma as a result of asbestos exposure. I have reviewed the materials, in this case, to determine the potential role, if any, of cosmetic talcum powder containing products from Johnson & Johnson ("Johnson's Baby Powder" and "Shower to Shower") that were allegedly purchased at Wal-Mart locations, Avon ("Avon Deep Woods," "Avon Musk," "Avon Spicy," "Timeless," "Soft Musk," "Cotillion," "Birds of Paradise," and "Skin So Soft"), Vi-Jon ("Equate"), Estée Lauder Companies ("ELC" for "White Linen"), Gold Bond and Ammens products allegedly bottled by PTI Union LLC, and cosmetic talc allegedly produced by IMI-Fabi, LLC, IMI Fabi (USA), LLC and IMI Fabi (Diana) LLC, allegedly containing asbestos, as a cause of Mr. Perry's disease. This supplemental report reflects additional materials that I have received and reviewed since the submission of my initial report on Mr. Perry on 27 June 2024 and should be read in conjunction with that report.

Please refer to the appendices at the conclusion of this supplemental report for an updated list of case materials that I have received and reviewed in this matter.

EXPERT REPORTS.**Peterson, Michael, M.E.M., DABT.¹**

Mr. Peterson reviewed case materials pertaining to Mr. Perry. It is Mr. Peterson's opinion that the scientific evidence does not support that exposure to Gold Bond and Ammen's cosmetic talc products increases the risk of mesothelioma. Mr. Peterson opined that even if Gold Bond and Ammen's cosmetic talc did contain trace asbestiform amphibole or serpentine minerals, this would not materially impact his conclusions. Mr. Peterson further notes that if he assumes that asbestiform amphibole or serpentine minerals were present in cosmetic talc products, then he would have to assume that the same non-talc minerals would be present in the cosmetic- and industrial-type talcs used in animal studies, as well as the talc to which miners and millers were exposed. He noted that given the negative results of the animal and epidemiology studies, and assuming that non-talc minerals were present in cosmetic talcs, he reasonably concludes that the levels were so low as to not increase the risk of mesothelioma. Mr. Peterson noted that this finding is consistent with risk calculations performed in the regulatory and peer-reviewed literature using conservative assumptions. Mr. Peterson stated that systematic review of the relevant scientific and peer-reviewed literature and the evidence from animal toxicology, epidemiology, exposure, and mechanistic studies of talc, it is his opinion that exposure to Gold Bond and Ammen's cosmetic talc products could not have increased Mr. Perry's risk of mesothelioma.

Mr. Peterson also identified possible occupational exposure to commercial amphibole asbestos during hotel renovations which occurred during his employment at various hotels. He noted that he was not able to determine the types of asbestos Mr. Perry might have been exposed to during his employment. Mr. Peterson opined that assuming Mr. Perry was exposed to at least some commercial amphibole asbestos (amosite and/or crocidolite) during the renovations, these exposures may have increased his risk of mesothelioma. If these exposures can be ruled out, it is likely that his mesothelioma occurred spontaneously. Mr. Peterson also noted that there is also the possibility that Mr. Perry has a genetic predisposition to cancer, as multiple first-degree relatives were also diagnosed with cancer.

Druschel, Gregory, PhD.²

Dr. Druschel evaluated plaintiffs' experts' reports on their findings of alleged asbestiform amphibole and chrysotile in commercial talc products and other samples assessing the veracity of the analytical approaches used and if they support positive identification of asbestiform amphiboles or chrysotile in talc samples. Dr. Druschel evaluated reports regarding Gold Bond powder products. Dr. Druschel opined that Dr. Longo's techniques lack sufficient precision, and are extremely susceptible to false positives for asbestos minerals in a talc matrix. Dr. Druschel further opined that the scientific evidence presented in plaintiffs' experts' reports is inconsistent, often with a low level of analytical quality, with a lack of precision necessary for the task, often done so poorly as to render the information useless, and does not support the conclusion, in any instance, of asbestiform amphibole or chrysotile presence in the samples analyzed.

¹ Expert Report of Michael Peterson, M.E.M., DABT, on behalf of PTI Union, LLC, dated 27 June 2024.

² Expert Report of Dr. Gregory K. Druschel, Ph.D., on behalf of PTI Union, LLC, dated 26 June 2024.

With regard to the likelihood of trace asbestiform amphiboles or chrysotile associated with the talc deposits of SW Montana or SW China, Dr. Druschel opined that thermodynamics dictates amphibole mineralization is impossible at these conditions, tectonics dictates chrysotile formation is impossible at these conditions. Further, he stated that if trace amphiboles or chrysotile are found in these samples (and here he noted that analytical work he has reviewed to date shows NO evidence of either) it is far more likely that small amount of asbestos mineral came from airborne dusts not related at all to the ore deposits, but rather contamination of the material sometime between excavation and analysis of the bottles in question.

ASSESSMENT AND CONCLUSIONS.

The allegation in this case is that Mr. Perry has pleural mesothelioma that was caused by cosmetic talc believed to also contain asbestos. I have assumed that the diagnosis of pleural mesothelioma is correct. Based on the materials available in this case, Mr. Perry does not have conditions such as diffuse pleural thickening or bilateral calcified pleural plaques which, if present, could be compatible with prior asbestos exposure. He does not have asbestosis.

In particular, I assessed the evidence in this case that asbestos as a potential contaminant of cosmetic talc produced and/or distributed by Johnson & Johnson, Avon, Vi-Jon, Estée Lauder, Gold Bond, Ammens IMI-Fabi, LLC, IMI Fabi (USA), LLC, and/or IMI-Fabi (Diana) could have been responsible for causing pleural mesothelioma in Mr. Perry. In this case, there is no objective evidence available that shows that Mr. Perry had any asbestos exposure from his alleged use of cosmetic talc produced and/or distributed by Johnson & Johnson, Avon, Vi-Jon, Estée Lauder, Gold Bond, Ammens, IMI-Fabi, LLC, and/or IMI-Fabi (Diana). There is no epidemiological evidence that the use of cosmetic talc produced and/or distributed by Johnson & Johnson, Avon, Vi-Jon, Estée Lauder, Gold Bond, Ammens, IMI-Fabi, LLC, IMI Fabi (USA), LLC, and/or IMI-Fabi (Diana) causes mesothelioma.

According to the testimony of Mr. Perry, his exposure to Johnson's Baby Powder was from his own personal use, his application to his husband, his husband's application to himself in his proximity, his mother's application to herself in his proximity, and his mother's application directly to him. Mr. Perry's exposure to Avon cosmetic talcum powder products was from playing with his father's container of powder and from being in proximity to his mother while she applied powder to herself. Mr. Perry's exposure to Vi-Jon cosmetic talcum powder products was from his application to himself and his application to his husband, and his husband's application to himself in Mr. Perry's proximity. Mr. Perry's exposure to Estée Lauder cosmetic talcum powder products was from being in proximity to his mother while she applied powder to herself. Mr. Perry's exposure to Gold Bond and Ammens cosmetic talcum powder products was from his own personal use and from applying powder to his shoes. Mr. Perry's exposure to cosmetic talc allegedly produced by IMI-Fabi, LLC, IMI Fabi (USA), LLC, and/or IMI Fabi (Diana), LLC was from talcum powder products since 2001.

Mr. Perry likely had no asbestos exposure from cosmetic talc produced and/or distributed by Johnson & Johnson, Avon, Vi-Jon, Estée Lauder, Gold Bond, Ammens, IMI Fabi (USA), LLC, and/or IMI Fabi (Diana), LLC, but even worst-case estimated exposures would have been to a dose too low to elevate his risk for mesothelioma. It is not plausible that his alleged exposures

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from cosmetic talc produced and/or distributed by Johnson & Johnson, Avon, Vi-Jon, Estée Lauder, Gold Bond, Ammens, IMI-Fabi, LLC, IMI Fabi (USA), LLC, and/or IMI-Fabi (Diana) caused his mesothelioma.

I have not seen evidence in this case of any significant exogenous exposure (including asbestos) that would raise his risk of developing pleural mesothelioma, though I cannot rule out a contribution from his claimed occupational exposures. If Mr. Perry did not have significant exogenous exposure from commercial amphibole asbestos, it is most likely that his mesothelioma developed spontaneously or was naturally occurring.

It is possible that Mr. Perry had an inherited genetic risk factor for cancer especially given his young age, and personal and family history of malignancies. However, there is no germline testing result available to confirm that.

This supplemental report is based on the information available to me at this time. Should additional information become available, I reserve the right to determine the impact, if any, of the new information on my opinions and conclusions, to revise my opinions and conclusions if necessary, and to rebut the opinions of any other experts that formulate an opinion in this matter.

Respectfully submitted,

A handwritten signature in black ink that reads "Gregory Diette". The signature is written in a cursive, flowing style.

Gregory B. Diette, M.D., M.H.S.

APPENDIX A: CASE MATERIALS AND OTHER DOCUMENTS RECEIVED.**Legal Documents/Materials:**

- Summons and Complaint
- First Amended Summons and Complaint
- Second Amended Summons and Complaint
- Plaintiff's Responses to Defendants' Master Set of Interrogatories and Requests for Production (Ex. 2)
- Plaintiffs' Responses to Defendants' Standard Interrogatories
- Plaintiffs' First Supplemental Responses to Defendants' Standard Interrogatories
- Plaintiffs' First Supplemental Responses to Defendants' Master Set of Interrogatories and Requests for Production (Ex. 2)

Depositions:

- Video-recorded Deposition of Michael L. Perry, Volume I, taken 10 October 2023, *with* Exhibits 1 through 14.
- Video-recorded Deposition of Michael L. Perry, Volume II, taken 11 October 2023, *with* Exhibits A through D.
- Video-recorded Deposition of Michael L. Perry, Volume III, taken 12 October 2023.
- Video-recorded Deposition of Michael L. Perry, Volume IV, taken 13 October 2023.

Expert Reports & Materials:

- Expert Report of Matthew S. Sanchez, on behalf of Johnson & Johnson, dated 06 June 2024.
- Expert Report of Matthew S. Sanchez, on behalf of Estée Lauder, dated 06 June 2024.
- Expert Report of Alan M. Segrave, PG, dated 17 June 2024.
- Expert Report of Christy A. Barlow, PhD, on behalf of Johnson & Johnson, dated 18 June 2024.
- Expert Report of R. Mark Bailey, PG, Laboratory Test Results for Avon Pavi Elle Perfumed Talc, Floral Fantasy, and 2 Odesseys, dated 27 December 2021.
- Expert Report of R. Mark Bailey, PG, Montana Talc Report on behalf of Avon, dated 12 June 2015.
- Expert Report of R. Mark Bailey, PG, Analysis of Avon Cotillion, dated 17 December 2019.
- Expert Report of R. Mark Bailey, PG, Laboratory Test Results for Avon Soft Musk and Topaze Perfumed Talc, dated 13 October 2021.
- Expert Report of R. Mark Bailey, PG, Laboratory Test Results for Avon To a Wild Rose, dated 19 January 2024.

- Murphy, North Carolina Talc Chart of Documents for Mark Bailey, PG, dated 20 August 2021.
- Expert Report of R. Mark Bailey, PG, on Asbestos in Talc Products from the Fontane Mine, Val Germanasca, Italy for Avon, dated 12 June 2020.
- Expert Report of R. Mark Bailey, PG, on Asbestos in Talc Products from the Hammondsville Mine, Vermont, USA for Avon, 16 November 2020.
- MAS Talcum Powder Analysis, Jeannine Henderson- Avon Wild Country, prepared by William E. Longo, PhD, CEO dated 25 October 2023.
- MAS Analysis of Avon Night Magic Talcum Powder, prepared by William E. Longo, PhD, and Mark W. Rigler, PhD, dated January 2019.
- MAS Report on Avon Talcum Powder Analysis with both Automated FESEM and ATEM, dated 12 March 2019.
- MAS Analysis Report of Chinese Talc Research Samples, prepared by William E. Longo, PhD, CEO dated 16 September 2020.
- MAS Analysis Report of Avon Occur Perfumed Talc, prepared by William E. Longo, PhD, dated 18 August 2021.
- MAS Talcum Powder Analysis of Avon and Clinique Containers, prepared by William E. Longo, PhD, dated 05 September 2021.
- MAS Talcum Powder Analysis of Montana Micro-Talc 1745 Retain Samples, prepared by William E. Longo, PhD, CEO dated 10 June 2022.
- MAS Talcum Powder Analysis of Avon Splits, prepared by William E. Longo, PhD, CEO dated 01 June 2022.
- MAS Talcum Powder Analysis of Historical Avon Splits: Wild Rose 1965, Cotillion 1961, & Persian Wood 1958, prepared by William E. Longo, PhD, CEO dated 01 June 2022.
- MAS Pfizer Treasure Mine Talc Analysis, prepared by William E. Longo, PhD, CEO dated 01 June 2022.
- MAS Talc Ore Samples Collected from the Eclipse Mine in Death Valley: Analyzed for Amphibole Asbestos by Transmission Electron Microscopy, prepared by William E. Longo, PhD, CEO dated 12 June 2022.
- MAS Talcum Powder Analysis of Rita Chapman Avon Powder Containers, prepared by William E. Longo, PhD, CEO dated 01 June 2022.
- MAS Supplemental Report Avon Talcum Powder Container Analysis for Asbestos, prepared by William E. Longo, PhD, CEO dated 30 September 2022.
- MAS Talcum Powder Analysis of Avon Powder Products, Project M71387 & M71587, prepared by William E. Longo, PhD, CEO dated 15 November 2022.
- MAS Talcum Powder Analysis of Avon Powder Products, Project M71560 & M71562, prepared by William E. Longo, PhD, CEO dated 15 November 2022.

- MAS Analysis Report of Avon Products, prepared by William E. Longo, PhD, dated 15 November 2022.
- MAS Supplemental Report Talcum Powder Analysis of Avon Powder Products, Project M71560 & M71562, prepared by William E. Longo, PhD, CEO dated 19 November 2022.
- MAS Talcum Powder Analysis of Avon Somewhere Powder, prepared by William E. Longo, PhD, CEO dated 20 September 2023.
- MAS Talcum Powder Analysis of Avon Split, prepared by William E. Longo, PhD, CEO dated 21 September 2023.
- MAS Avon Talcum Powder Analysis, prepared by William E. Longo, PhD, CEO dated 21 September 2023.
- MAS Talcum Powder Analysis of Solomon, Beth – Talc Splits, prepared by William E. Longo, PhD, CEO dated 16 February 2024.
- MAS Analysis Report of Avon Unforgettable Perfumed Talc, prepared by William E. Longo, PhD, dated 21 April 2017.
- Expert Report of Steven P. Compton, PhD, Investigation of Italian Talc Samples for Asbestos, dated 01 August 2017.
- Expert Report of Steven P. Compton, PhD, Investigation of Vermont Talc Samples for Asbestos, dated 23 April 2018.
- Expert Report of Steven P. Compton, PhD, Investigation of Montana Talc (American International Industries Microtalc 1745) for Asbestos, dated 15 March 2019.
- Expert Report of Steven P. Compton, PhD, Examination of Avon Talcum Powder for Asbestos Gail Welch Case, dated 29 May 2020.
- Expert Report of Steven P. Compton, PhD, Examination of 907 Talc Powder for Asbestos, dated 26 January 2024.
- Expert Report of Steven P. Compton, PhD, Examination of Vintage Avon Bunny Fluffpuff Talc in Rabbit-shaped Puff container for Asbestos, dated 19 May 2023.
- Expert Report of Steven P. Compton, PhD, Examination of Vintage Avon Unforgettable Talc in Shaker Container for Asbestos, dated 19 May 2023.
- Expert Report of Jennifer S. Pierce, MS, PhD, in the matter of Michael Perry regarding Avon, Inc., dated 19 June 2024.
- Affidavit of R. Mark Bailey, on behalf of Johnson & Johnson, dated 30 October 2023, with exhibits 1 through 16.
- MAS Expert Analysis Report of Estee Lauder Products by William E. Longo, PhD, CEO, dated 16 December 2022.
- Expert Report of R. Mark Bailey, PG, Transmission Electron Microscopy Analytical Test Report of Johnson & Johnson Baby Powder, dated 06 May 2021.

- Expert Report of R. Mark Bailey, PG, Transmission Electron Microscopy Analytical results for 3 talc archive batch samples on behalf of Johnson & Johnson, dated 08 September 2021.
- MAS 4th Supplemental MDL Report, Analysis of Non-Historical J&J's Talcum Powder Consumer Product Containers and J&J Chinese Historical Talc Retain Samples, by William E. Longo, PhD, CEO, dated 29 April 2024.
- MAS Supplemental #2 Expert Report on Below the Waist Application of Johnson & Johnson Baby Powder by William E. Longo, PhD, Mark W. Rigler, PhD, and William B. Egeland, MS, PG, dated January 2018.
- MAS Expert Report Rev #1 on Talcum Powder Application to Baby and Diaper Change II: A Hygiene Study by William E. Longo, PhD, William B. Egeland, MS, PG, and Martin Bennett, dated 28 June 2019.
- MAS Expert Report on Johnson's Baby Powder Application to Baby and Diaper Change: A Hygiene Study Supplemental by William E. Longo, PhD, William B. Egeland, MS, PG, and Martin Bennett, dated May 2020.
- Declaration of William Longo, PhD, dated 21 September 2021.
- Expert Report of Jennifer Sahmel, PhD, CIH, CSP, FAIHA, on behalf of Vi-Jon, dated 20 June 2024.
- Expert Report of Paul A. Nony, PhD, CIH, CSP, on behalf of Estée Lauder, dated 26 June 2024, *with* References.
- Expert Report of Michael Peterson, M.E.M., DABT, on behalf of PTI Union, LLC, dated 27 June 2024.
- Expert Report of Dr. Gregory K. Druschel, Ph.D., on behalf of PTI Union, LLC, dated 26 June 2024.

Other:

- Social Security Records of Michael Perry, 1979 through 2000.
- Social Security Records of Michael Perry, 1987 through 2023.
- Work History Affidavit.

Medical Documents/Materials:

- PERRY - MUSC 2.8.23-11.17.23
- PERRY - RSFP ROPER 2022-2023
- PERRY ROPER 5.19.17-7.1.23
- SC-PERRY MUSC radiology link
- Perry, Michael - Roper St. Francis (Dx Pathology Report 07.05.23) PERRY_SC_000014-000015 (3065538)

- Admission to Medical University of South Carolina dated 080823
- Admission to Palmetto Digestive Health Specialists dated 062623
- Cardiac testing
- Office notes of Charleston Oncology
- Office notes of Medical University of South Carolina (reverse chron)
- Office notes of Roper St. Francis Physician Partners
- Pathology reports
- Radiology reports
- Perry, Michael - Dr. Brian M. Lingerfelt (Medical 07.07.23)
- Perry, Michael - Edgepark Medical Supplies (Medical 07.07.23)
- Perry, Michael - Medical University of South Carolina (Pathology)
- Perry, Michael - MUSC (Pathology Report 08.18.23)
- Perry, Michael - MUSC Medical University of S. Carolina (Medical 07.08.23 - 08.18.23 Vol 1)
- Perry, Michael - MUSC Medical University of S. Carolina (Medical 07.08.23 - 08.18.23 Vol 2)
- Perry, Michael - MUSC Medical University of S. Carolina (Medical 07.08.23 - 08.18.23 Vol 3)
- Perry, Michael - MUSC Medical University of S. Carolina (Medical 08.22.23 - 12.26.23 Vol 1 - UC)
- Perry, Michael - MUSC Medical University of S. Carolina (Medical 08.22.23 - 12.26.23 Vol 2)
- Perry, Michael - MUSC Medical University of South Carolina (Medical Affidavit 07.08.23 - 08.18.23)
- Perry, Michael - Palmetto Digestive Disease Endoscopy Center (Medical 06.19.17 - 06.26.23)
- Perry, Michael - Palmetto Digestive Disease Endoscopy Center (Medical Affidavit 06.19.17 - 06.26.23)
- Perry, Michael - Pulmonology at MUSC Health Hollings Cancer Center (Medical 07.15.23 - 07.24.23)
- Perry, Michael - Pulmonology at MUSC Health Hollings Cancer Center (Medical Affidavit 07.15.23 - 07.24.23)
- Perry, Michael - Roper Hospital (Medical 03.01.21 - 06.30.23)
- Perry, Michael - Roper Hospital (Pathology)

- Perry, Michael - Roper St. Francis (Dx Pathology Report 07.05.23)
- Perry, Michael - Roper St. Francis Healthcare (Medical Vol 1 01.11.21 - 07.12.23)
- Perry, Michael - Roper St. Francis Healthcare (Medical Vol 2 01.11.21 - 07.12.23)
- Perry, Michael - Roper St. Francis Healthcare (Medical
- Admission to Medical University of South Carolina dated 07.24.23.
- Admission to Palmetto Digestive Health Specialists dated 04.10.19.
- Admission to Palmetto Digestive Health Specialists dated 06.05.23.
- Admission to Palmetto Digestive Health Specialists dated 06.19.17.
- Admission to Palmetto Digestive Health Specialists dated 07.12.17.
- Admission to Palmetto Digestive Health Specialists dated 08.09.17.
- Admission to Palmetto Endoscopy Center dated 01.20.14.
- Admission to Roper Hospital dated 06.30.23.
- Office notes of Medical University of South Carolina.
- Pathology reports; 02.25.10.
- Radiology reports; 06.11.17.
- Office notes of Medical University of South Carolina (reverse chron).
- Radiology reports; 12.05.23.
- Radiology Materials – Refer to **APPENDIX C** for list of studies received on disc format
 - 03 disc(s) on 10 May 2024 from Medical University of South Carolina.
 - 01 disc(s) on 04 June 2024 from Medical University of South Carolina.

APPENDIX B: LITERATURE CONSIDERED, REPORTS REVIEWED AND OTHER RELIANCE MATERIALS.

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APPENDIX C: RADIOLOGY STUDIES, AS RECEIVED ON COMPACT DISCS.**Medical University of South Carolina, 20 studies:**

- NM Pulmonary Ventilation Perfusion VQ, Accession Number: 21078587, dated 07/14/2023.
- MRI Brain W WO Contrast, Accession Number: 21076525, dated 07/17/2023.
- MRI Chest W WO Contrast, Accession Number: 21076526, dated 07/17/2023.
- PET CT Skull Base to Midthigh, Accession Number: 21053965, dated 07/18/2023.
- XR Chest 1 View Portable, Accession Number: 21178471, dated 08/08/2023.
- XR Chest 1 View Portable, Accession Number: 21178636, dated 08/08/2023.
- XR Chest AP Portable, Accession Number: 21178863, dated 08/09/2023.
- XR Chest AP Portable, Accession Number: 21182695, dated 08/10/2023.
- XR Chest AP Portable, Accession Number: 21187659, dated 08/11/2023.
- XR Chest AP Portable, Accession Number: 21192101, dated 08/12/2023.
- XR Chest 2 Views, Accession Number: 21194509, dated 08/13/2023.
- XR Chest 2 Views, Accession Number: 21195964, dated 08/14/2023.
- XR Chest 2 Views, Accession Number: 21200519, dated 08/15/2023.
- XR Chest 2 Views, Accession Number: 21201843, dated 08/15/2023.
- XR Chest PA and Lateral, Accession Number: 21266398, dated 09/01/2023.
- CT Chest W Contrast, Accession Number: 21290447, dated 09/29/2023.
- CT Chest W Contrast, Accession Number: 21567301, dated 12/05/2023.
- RAD ONC PLANNING, Accession Number: 21555596, dated 01/02/2024.
- RAD ONC PLANNING, Accession Number: 21873777, dated 01/31/2024
- CT Chest W Contrast, Accession number: 21822953, dated 04/29/2024.

EXHIBIT 3

STATE OF SOUTH CAROLINA : IN THE COURT OF COMMON PLEAS

:
COUNTY OF RICHLAND : FOR THE FIFTH JUDICIAL CIRCUIT

SARAH J. PLANT and :

PARKER PLANT, :

Plaintiffs, :

v. : C/A NO. 2022-CP-40-1265

AVON PRODUCTS, INC., :

et al. :

Defendants. :

KELLY PAYNE CLARK and :

SHANNON PAYNE LANCASTER,:

as Co-Executors of the :

Estate of SHELBY :

LINVILLE PAYNE, deceased:

Plaintiffs, :

v. : C/A NO. 2022-CP-40-01281

3M COMPANY, et al., :

Defendants. :

Deposition of GREGORY B. DIETTE, MD, MHS

Reported by:

Adam D. Miller, Registered Professional Reporter

Gregory B. Diette, MD, MHS
February 03, 2023

ELECTRONICALLY FILED - 2024 Jul 11 12:44 AM - RICHLAND - COMMON PLEAS - CASE#2023CP4004072

Page 2 1 2 3 Deposition of GREGORY B. DIETTE, MD, MHS 4 5 Via Zoom Videoconferencing 6 7 Friday, February 3, 2023 8 11:00 a.m. 9 10 - - - - - 11 12 APPEARANCES: 13 On Behalf of Plaintiffs: 14 BENJAMIN H. ADAMS, ESQUIRE 15 badams@dobslegal.com 16 DAVID C. HUMEN, ESQUIRE 17 dhumen@dobslegal.com 18 RACHEL A. GROSS, ESQUIRE 19 rgross@dobslegal.com 20 DEAN OMAR BRANHAM SHIRLEY, LLP 21 302 North Market Street, Suite 300 22 Dallas, Texas 75202 23 214.722.5990 24 25	Page 4 1 On Behalf of Rite Aid of South Carolina, Inc.: 2 R. SCOTT WALLINGER, JR., ESQUIRE 3 swallinger@barnwell-whaley.com 4 BARNWELL WHALEY PATTERSON & HELMS, LLC 5 211 King Street, Suite 300 6 Charleston, South Carolina 29401 7 843.577.7700 8 On Behalf of Mary Kay Inc.: 9 WILLIAM M. WILSON, III, ESQUIRE 10 bwilson@wyche.com 11 WYCHE, P.A. 12 200 East Broad Street, Suite 400 13 Greenville, South Carolina 29601 14 864.242.8200 15 On Behalf of Coty, Inc., Noxell Corporation, The Procter 16 & Gamble Company, and Wyeth Holdings LLC: 17 BRIANNA BAILEY, ESQUIRE 18 brianna.bailey@cs-law.com 19 COSMICH SIMMONS & BROWN, PLLC 20 One Eastover Center 21 100 Vision Drive, Suite 200 22 Jackson, Mississippi 39211 23 601.863.2100 24 25
Page 3 1 On Behalf of Colgate-Palmolive Company, as 2 successor-in-interest to The Mennen Company: 3 KATHERINE A. LAWLER, ESQUIRE 4 katherine.lawler@nelsonmullins.com 5 and ASHLEY WETZEL, ESQUIRE 6 NELSON MULLINS RILEY & SCARBOROUGH LLP 7 100 S. Charles Street, Suite 1600 8 Baltimore, Maryland 21201 9 443.392.9400 10 On Behalf of Whittaker, Clark & Daniels, Inc.: 11 BRUCE T. BISHOP, ESQUIRE 12 bbishop@wilsav.com 13 WILLCOX & SAVAGE 14 Wells Fargo Center 15 440 Monticello Avenue 16 Suite 2200 17 Norfolk, Virginia 23510 18 757.628.5573 19 On Behalf of Topco Associates, LLC: 20 ANA T. REEG, ESQUIRE 21 Areeg@hpylaw.com 22 HAWKINS PARNELL & YOUNG 23 1 Post Street, Suite 2400 24 San Francisco, California 94104 25 415.766.3200	Page 5 1 On Behalf of Goulds Pumps, LLC, Grinnell, LLC, ITT LLC, 2 and Zurn Industries, LLC: 3 ROBERT O. MERIWETHER, ESQUIRE 4 robert.meriwether@nelsonmullins.com 5 NELSON MULLINS RILEY & SCARBOROUGH LLP 6 Meridian 7 1320 Main Street, 17th Floor 8 Columbia, South Carolina 29201 9 800.237.2000 10 On Behalf of Walmart, Inc.: 11 RANDI LYNN ROBERTS, ESQUIRE 12 rlroberts@gaffneylewis.com 13 GAFFNEYLEWIS LLC 14 3700 Forest Drive, Suite 400 15 Columbia, South Carolina 29204 16 803.790.8838 17 -and- 18 STEPHEN H. BARRETT, ESQUIRE 19 stephen.barrett@us.dlapiper.com 20 DLA PIPER US LLP 21 One Liberty Place 22 1650 Market Street, Suite 4900 23 Philadelphia, Pennsylvania 19103 24 25

Gregory B. Diette, MD, MHS
February 03, 2023

Page 6 1 On Behalf of Brenntag North America Inc.: 2 KELLY L. NEAR, ESQUIRE 3 KLN@maronmarvel.com 4 MARON MARVEL BRADLEY ANDERSON & TARDY LLC 5 259 Seven Farms Drive, Suite 300 6 Daniel Island, South Carolina 29492 7 843.727.0001 8 On Behalf of Color Techniques, Inc. and Bahnson, Inc.: 9 JULIE FEKETE, ESQUIRE 10 jfekete@grsm.com 11 GORDON REES SCULLY MANSUKHANI, LLP 12 40 Calhoun Street, Suite 350 13 Charleston, South Carolina 29401 14 843.278.5900 15 On Behalf of Avon Products, Inc. (Payne case): 16 MADELYN IUOLO, ESQUIRE 17 miulo@foleymansfield.com 18 FOLEY & MANSFIELD 19 86 Chambers Street, Suite 202 20 New York, New York 10007 21 212.421.0436 22 23 24 25										Page 8 1 On Behalf of International Paper Company and 2 Weyerhaeuser Co. (Payne case): 3 RUTH M. HUSKEY, ESQUIRE 4 Ruth.Maron@formanwatkins.com 5 FORMAN WATKINS & KRUTZ LLP 6 210 East Capitol Street, Suite 2200 7 Jackson, Mississippi 39201-2375 8 601.960.8600 9 ----- 10 INDEX 11 DEPONENT: GREGORY B. DIETTE, MD, MHS 12 EXAMINATION BY: PAGE 13 ATTORNEY ADAMS 11 14 ----- 15 EXHIBITS 16 NAME DESCRIPTION PAGE 17 Exhibit 1 2/1/23 Diette Report re Plant 16 18 Exhibit 2 2/1/23 Diette Report re Payne 16 19 Exhibit 3 Plant Medical Record Excerpt 31 20 Exhibit 4 Rough Draft Transcript of the 36 21 Deposition of Taylor Ripley, MD 22 Exhibit 5 7/12/19 Poye Report 56 23 Exhibit 6 Diette Notes re Eric Johnson in 60 24 the Plant Case 25									
Page 7 1 On Behalf of Vi-Jon, LLC (Plant case): 2 ANGELA G. STRICKLAND, ESQUIRE 3 angela.strickland@bowmanandbrooke.com 4 BOWMAN AND BROOKE LLP 5 1441 Main Street, Suite 1200 6 Columbia, South Carolina 29201 7 803.726.7420 8 On Behalf of Chattem, Inc.: 9 STEVEN J. PUGH, ESQUIRE 10 SPugh@RichardsonPlowden.com 11 RICHARDSON PLOWDEN ROBINSON, P.A. 12 1900 Barnwell Street 13 Columbia, South Carolina 29201 14 803.771.4400 15 On Behalf of CVS Pharmacy, Inc., Walgreen Co., 16 Winn-Dixie Stores, Inc. (Payne case); and Walgreen Co., 17 Winn-Dixie Stores, Inc., Southeastern Grocers (Plant 18 case): 19 AMY HARMON GEDDES, ESQUIRE 20 AGeddes@nexsenpruet.com 21 NEXSEN PRUET, LLC 22 1230 Main Street, Suite 700 23 Columbia, South Carolina 29201 24 Post Office Box 2426 (29202) 25 803.771.8900										Page 9 1 Exhibit 7 Diette Notes re Dr. Maddox in 60 2 the Plant Case 3 Exhibit 8 Diette Notes re Patrice Johnson 61 4 in the Plant Case 5 Exhibit 9 Diette Notes re the Deposition 61 6 of Sarah Plant 7 Exhibit 10 Diette Legal and Employment 61 8 Notes in the Plant Case 9 Exhibit 11 Diette Medical Notes in the 62 10 Plant Case 11 Exhibit 12 Diette Pulmonary Function Test 62 12 Summary Chart in the Plant Case 13 Exhibit 13 Diette CV 62 14 Exhibit 14 Diette Testimony List 62 15 Exhibit 15 Diette Fee Schedule 63 16 Exhibit 16 Diette Invoices in the Plant 63 17 Case 18 Exhibit 17 Diette Medical Notes in the 65 19 Payne Case 20 Exhibit 18 Diette Legal Notes in the Payne 65 21 Case 22 Exhibit 19 Diette Notes re the Deposition 65 23 of Shannon Payne Lancaster 24 Exhibit 20 Diette Notes re the Deposition 66 25 of Kelly Payne Clarke									

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1 Exhibit 21 Diette Pulmonary Function Test 66 2 Results, Summary Chart in the 3 Payne Case 4 Exhibit 22 Diette Invoices in the Payne 66 5 Case 6 Exhibit 23 Diette Notice of Deposition in 67 7 the Plant Case 8 Exhibit 24 Diette Notice of Deposition in 67 9 the Payne Case 10 Exhibit 25 11/16/21 Diette Report re Moore 83 11 Exhibit 26 8/9/22 Gordon Report re Moore 92 12 Exhibit 27 5/31/22 Dodson Report re Moore 95 13 Exhibit 28 Colgate-Palmolive's Objections 129 14 to the Notices 15 16 17 18 19 20 21 22 23 24 25	Page 10	1 expert opinions that you've reached in the Payne 2 case? 3 A. I am. 4 Q. Are you prepared to tell us about 5 each and every one of the expert opinions you've 6 reached within a reasonable degree of medical 7 certainty? 8 A. Yeah, I hope so. 9 Q. Okay. Is there any reason you can't 10 give us your opinions today? 11 A. No. 12 Q. Are there any documents you wanted 13 that you didn't receive? 14 A. None that I know that exist. I mean, 15 just in general, I have, you know, an interest 16 in documents that could exist, you know, if they 17 come up later, I guess. 18 Q. Are there any questions you had that 19 weren't answered? 20 A. By lawyers or...? 21 Q. Yeah. 22 A. No, there weren't any. 23 Q. If I ask a question that's vague or 24 ambiguous, will you let me know? 25 A. A hundred percent.	Page 12
1 GREGORY B. DIETTE, MD, MHS, having 2 first been duly sworn according to law, was 3 examined and testified as follows: 4 BY ATTORNEY ADAMS: 5 Q. Dr. Diette, can you tell us your full 6 name for the record. 7 A. Sure. Gregory Bruce Diette. 8 Q. You've been retained as an expert 9 witness in the Sarah Plant case? 10 A. That's correct. 11 Q. And the Shelby Payne case? 12 A. That is correct. 13 Q. By who? 14 A. Well, let's see. For Miss Payne, 15 it's Colgate-Palmolive and Mennen and Avon. 16 Let me just be sure -- and for 17 Miss Plant, Colgate-Palmolive and Whittaker, 18 Clark & Daniels. 19 Q. Anyone else in either case? 20 A. No. 21 Q. Are you prepared to give all your 22 expert opinions that you've reached in the Plant 23 case? 24 A. I am. 25 Q. Are you prepared to give all your	Page 11	1 Q. If ask a question you don't 2 understand, will you let me know? 3 A. I will. 4 Q. If I ask a question that assumes a 5 fact that's untrue, will you let me know? 6 A. I'm not sure. Like, I don't know if 7 I'll know that that's the case. 8 Q. But if I say something like "When did 9 you stop beating your wife," would you let me 10 know that I've assumed a fact that isn't true, 11 that kind of thing? 12 A. If it's clear like that, I will. 13 Q. Thanks. Is it your opinion, within a 14 reasonable degree of medical certainty, that 15 Sarah Plant was exposed to asbestos? 16 A. No. I think it's possible. But I 17 don't have enough information to show that she 18 was. 19 Q. Is it one of your opinions in this 20 case, to a reasonable degree of medical 21 certainty, that Shelby Payne was exposed to 22 asbestos? 23 A. I think it's similar. Like I know 24 that there's allegations that she was. But I 25 don't have enough information for me to say that	Page 13

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Page 14 1 that's a fact. 2 Q. Is it your opinion in this case, 3 within a reasonable degree of medical certainty, 4 that Sarah Plant's mesothelioma was caused by 5 asbestos? 6 A. Based on the information I have right 7 now, I cannot say that it was. 8 Q. Is it one of your opinions in this 9 case, within a reasonable degree of medical 10 certainty, that Shelby Payne's mesothelioma was 11 caused by asbestos? 12 A. Again, you know, based on the 13 information I have, I can't make that statement 14 that it was caused by asbestos. 15 Q. Is it one of your opinions, within a 16 reasonable degree of medical certainty, that 17 Sarah Plant's mesothelioma was caused by 18 exposure to asbestos from her father? 19 A. No, I don't have enough information 20 to say that that's the case. 21 Q. Is it one of your opinions, within a 22 reasonable degree of medical certainty, that 23 Sarah Plant's mesothelioma was caused by 24 exposure to asbestos from pottery? 25 A. Again, I know that there's that	Page 16 1 husband. 2 Q. Is it one of your opinions, within a 3 reasonable degree of medical certainty, that 4 Miss Payne's mesothelioma formed spontaneously? 5 A. It is. 6 Q. Is it one of your opinions, within a 7 reasonable degree of medical certainty, that 8 Miss Payne's mesothelioma was naturally 9 occurring? 10 A. It is. 11 ATTORNEY ADAMS: I'm going to attach 12 as Exhibit 1 your report in the Sarah 13 Plant case dated February 1st, 2023. 14 (Exhibit 1 was marked for 15 identification.) 16 ATTORNEY ADAMS: And I'll attach as 17 Exhibit Number 2 Dr. Diette's report in 18 the Shelby Payne case dated February 2nd, 19 2023. 20 (Exhibit 2 was marked for 21 identification.) 22 BY ATTORNEY ADAMS: 23 Q. Do you have those reports, Doctor? 24 A. I do. 25 Q. Are all of your opinions that you
Page 15 1 allegation, but I don't have enough information 2 for me to say that she was exposed to asbestos 3 from her pottery work. 4 Q. Is it one of your opinions, within a 5 reasonable degree of medical certainty, that 6 Sarah Plant's mesothelioma was spontaneous? 7 A. Yeah, I think I use the term 8 "naturally occurring" for her because I think 9 that -- I think -- you know, I'm referring to 10 spontaneous mutations but also a contribution 11 from her germline genetic defect. 12 Q. Is it one of your opinions, within a 13 reasonable degree of medical certainty, that 14 Sarah Plant's mesothelioma was naturally 15 occurring? 16 A. Yes. 17 Q. Is it one of your opinions, within a 18 reasonable degree of medical certainty, that 19 Miss Payne was exposed to asbestos from her 20 husband? 21 A. You know, it's similar to, I guess, 22 what we talked about with these other exposures. 23 I know that it's been mentioned in the 24 materials. But I don't have enough information 25 to say that she was exposed to asbestos from her	Page 17 1 have reached as of today, February 3rd, 2023, 2 contained within those two reports? 3 A. Yeah, I think all the main or basic 4 opinions. You know, there sometimes can be 5 minor opinions that are supporting that I didn't 6 list. But my major, my major opinions that I 7 expect to have in both of these reports are in 8 there. 9 Q. Are there any opinions in the Payne 10 or Plant case you can tell me about now that are 11 not contained in the two reports? 12 ATTORNEY LAWLER: Objection to form. 13 THE WITNESS: No, I'm not aware of 14 any right now. I'm just imagining that 15 there could be a question, you know, that 16 elicits an opinion. And I may not have 17 written it in the report. 18 BY ATTORNEY ADAMS: 19 Q. One of your conclusions in the 20 report -- let's start with the Sarah Plant 21 case -- is [as read]: Based on the available 22 medical and scientific literature, it is not 23 plausible that asbestos as a potential 24 contaminant of talc in Cashmere Bouquet cosmetic 25 talcum powder or cosmetic talc allegedly

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Page 18 1 distributed by Whittaker, Clark & Daniels to 2 Avon could have caused Miss Plant to develop 3 mesothelioma; correct? 4 A. That's correct. 5 Q. Where did the talc Whittaker, Clark & 6 Daniels supplied to Avon come from? 7 ATTORNEY LAWLER: Object to form. 8 THE WITNESS: It's whatever's in 9 Mr. Seagrave's report. It's detailed 10 there. I mean, I didn't memorize it. But 11 I could pull out his report and see what 12 he said. 13 BY ATTORNEY ADAMS: 14 Q. Sure. 15 A. Would you like me to do that? 16 Q. Please. 17 A. Okay. 18 So I have his report. So it looks 19 like he, he detailed talc deposits from Val 20 Chisano in Italy; Murphy, North Carolina; 21 Southwestern Montana; Alpine Alabama; Southern 22 Vermont; and Guangxi, China. And I think he 23 also mentioned France as the general sources 24 that he considered. 25 And then for Avon in particular, I	Page 20 1 considered in his report for all of the sources 2 together, including those that went to Avon. 3 But I haven't -- I don't think I 4 remember exactly whether it's every single one 5 of those or just some subset of those that he 6 links with Avon. 7 Q. Okay. But Italy -- okay. So what is 8 your understanding of where the talc that 9 Whittaker, Clark & Daniels supplied to Avon came 10 from? Is it just based on Mr. Seagrave's 11 report? 12 A. It is. 13 Q. Okay. And based on Mr. Seagrave's 14 report, the talc Whittaker, Clark & Daniels 15 supplied to Avon came from Italy, 16 North Carolina, Southwestern Montana, Southern 17 Vermont, China, and France or some subset of 18 those regions; correct? 19 A. Yes. 20 ATTORNEY LAWLER: Object to form. 21 THE WITNESS: Correct. Especially 22 with "or some subset," right. I think 23 that's the full universe potentially. I'd 24 have to go back and look carefully at his 25 report to see which of those he
Page 19 1 think he's got -- let's see if I can figure this 2 out. 3 I think it's some subset of that. 4 But that's the universe of potential, potential 5 sources. 6 Q. Italy, North Carolina, Southern 7 Montana, Vermont, China, and France? 8 A. Do we leave one out? Did you say 9 North Carolina? 10 Q. I did. 11 A. Okay. And Southern Vermont? 12 Q. I just have Vermont. I had Southern 13 Montana. 14 A. I got -- I have Southwest Montana and 15 then Southern Vermont, from his report. 16 Q. Got it. Let me just make sure I have 17 it. 18 So it's your understanding, 19 Dr. Diette, that the talc Whittaker, Clark & 20 Daniels supplied to Avon at issue in the Sarah 21 Plant case came from Italy, North Carolina, 22 Southwestern Montana, Southern Vermont, China, 23 and France? 24 A. No. It's not my opinion. My opinion 25 is that those are the sources that Mr. Seagrave	Page 21 1 specifically linked to Avon and not 2 necessarily to some other company or 3 product. 4 BY ATTORNEY ADAMS: 5 Q. But no other regions that you're 6 aware of -- strike that. 7 Other than what I just listed, there 8 are no other regions you're aware of where talc 9 came from that Whittaker, Clark & Daniels 10 supplied to Avon at issue in the Sarah Plant 11 case; am I correct? 12 A. I think so. I didn't listen 13 carefully as you read off the locations. But 14 again, it's the ones that he's listed literally 15 in his report. So assuming you said all of 16 those that I said, then that's exactly right. 17 Q. Okay. Dr. Diette, I need you to try 18 to listen very carefully. This is important to 19 me. 20 The regions were you understand the 21 talc Whittaker, Clark & Daniels supplied to Avon 22 are -- I don't even -- I don't like that 23 question. Let me try again. 24 Your understanding of where the talc 25 Whittaker, Clark & Daniels supplied to Avon came

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Page 22 1 from -- I don't like that either. Let me try a 2 third time. 3 It's your understanding that the talc 4 Whittaker, Clark & Daniels supplied to Avon came 5 from Italy, North Carolina, Southwestern 6 Montana, Southern Vermont, China, and France, or 7 some subset of those regions; correct? 8 ATTORNEY LAWLER: Object to form. 9 THE WITNESS: Yeah, you left out 10 Alabama. 11 BY ATTORNEY ADAMS: 12 Q. Ah, that's good. 13 A. But I can say my answer would be yes 14 if you also include Alabama in your question. 15 Q. Got it. You're not aware of 16 Whittaker, Clark & Daniels supplying talc to 17 Avon from any other region other than those that 18 I just listed; correct? 19 ATTORNEY LAWLER: Object to form. 20 THE WITNESS: That's correct. 21 BY ATTORNEY ADAMS: 22 Q. And the basis of your understanding 23 of where Whittaker, Clark & Daniels got the talc 24 it supplied to Avon is Mr. Seagrave's report; 25 correct?	Page 24 1 A. I think I've seen, I've seen one 2 study that I think's an exposure study. But not 3 a traditional epidemiology study. 4 Q. So you're not aware of any 5 traditional epidemiology studies performed on 6 any miners and millers of talc in Southwestern 7 Montana? 8 A. Correct. 9 Q. I know you're aware of epidemiology 10 studies performed on miners and millers of talc 11 in Italy and Vermont; correct? 12 A. You are. 13 Q. Are there epidemiology studies of 14 miners and millers of talc in France? 15 A. There are. 16 Q. That's what I thought. 17 Another one of your opinions in your 18 report is that [as read]: Miss Plant had a 19 genetic predisposition to cancer, BRCA2, which 20 increased her risk of developing malignancies, 21 including mesothelioma. 22 Correct? 23 A. That is correct. 24 Q. Did BRCA2 cause Miss Plant's 25 mesothelioma?
Page 23 1 THE WITNESS: That is correct. 2 BY ATTORNEY ADAMS: 3 Q. Anything else? 4 A. No. 5 Q. Are you aware of any epidemiology 6 studies performed on the miners and millers of 7 talc in Alabama? 8 A. I am not. 9 Q. Are you aware of any epidemiology 10 studies performed on the miners and millers of 11 talc in China? 12 A. Sure. I mean -- but there's 13 different epidemiology studies done in different 14 regions at different times. 15 Q. Are you aware of any specifically 16 done on miners and millers in China? 17 A. I can't recall -- I can't recall any 18 right now. 19 Q. Are you aware of any epidemiology 20 studies performed on the miners and millers of 21 talc in North Carolina? 22 A. I have not seen any. 23 Q. Are you aware of any epidemiology 24 studies performed on the miners and millers of 25 talc in Southwestern Montana?	Page 25 1 A. I think it may have contributed to 2 her development of mesothelioma. 3 Q. Is it one of your opinions, to a 4 reasonable degree of scientific certainty, that 5 Miss Plant's BRCA2 genetic mutation was the sole 6 cause of her mesothelioma? 7 ATTORNEY LAWLER: Object to form. 8 THE WITNESS: I don't think so. 9 I'm just trying to make sure I 10 understand your question. I guess, I 11 guess my answer would be no because I 12 think what she has is a DNA repair gene 13 abnormality. 14 And so I think more likely it would 15 be that she had a spontaneous mutation 16 that couldn't be repaired. So the BRCA2 17 defect contributed. 18 But I wouldn't be able to say that 19 all by itself, you know, that it 20 literally, you know, caused the cancer. 21 BY ATTORNEY ADAMS: 22 Q. Are you aware of a study that 23 concludes BRCA2 causes mesothelioma in the 24 absence of asbestos exposure? 25 ATTORNEY LAWLER: Object to form.

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Page 26 1 THE WITNESS: Well, I think we have 2 to think about what "cause" means. You 3 know, there are studies that have found 4 association of BRCA2 with mesothelioma 5 cases, including in people with no 6 asbestos exposure. 7 And, you know, for that type of 8 germline mutation it's been shown that 9 those are more likely in people with 10 minimal or no asbestos exposure. So it 11 fits with the concept I think you're 12 asking about. 13 BY ATTORNEY ADAMS: 14 Q. Can you name any of those studies? 15 A. Sure. No, I have them listed in my 16 report. 17 Q. Right. Can you point me to them? 18 A. Uh-huh. So I think we'll find most 19 of what we're looking for on page 31 and maybe 20 into 32 of the report. And then the articles 21 that I've listed there -- let me just see -- 22 that in sum sort of cover this topic are the 23 number 261 through number 266, as the, the 24 referenced citations at the bottom. 25 Q. And this is for Sarah Plant --	Page 28 1 A. I don't, I don't have any others to 2 point to. 3 Q. Okay. Do you know whether or not any 4 of the authors in any of the studies 261 to 266 5 have been paid by talc companies, asbestos 6 companies, or lawyers for the same? 7 A. I don't know one way or the other. I 8 haven't looked at the full list of each and 9 every author. 10 Q. Okay. Have you reviewed Miss Plant's 11 medical records in this case? 12 A. I have. 13 Q. Do you know who Dr. Taylor Ripley is? 14 A. I don't remember doctor by doctor. I 15 mean, I read all the notes, but I didn't 16 memorize, you know, who the doctors were. 17 Q. Okay. Have you reviewed the 18 deposition of Dr. Taylor Ripley that was taken 19 in this case? 20 A. I don't think I have it. 21 Q. Who provided you the case-specific 22 materials in this case? 23 A. The law firms involved in this case. 24 Q. For Colgate, Mennen, Whittaker, 25 Clark & Daniels, and Avon?
Page 27 1 A. I hope so. 2 Q. -- the report? 3 A. Yeah, that's the one I'm looking at. 4 Q. Okay. And it's your testimony that 5 the articles referenced in the footnotes 261 to 6 266 of your report in the Sarah Plant case state 7 that BRCA2 genetic mutation contributes to the 8 development of mesothelioma in individuals not 9 exposed to asbestos? 10 A. Well, what you said isn't a quote 11 from one of the studies. But what the studies 12 show in aggregate -- I can pull out the specific 13 ones -- show that BRCA2 and other similar 14 germline mutations are associated with people 15 who lack an asbestos exposure history. 16 So they don't say it the way you did, 17 but that's the meaning of that. 18 Q. And that's what the studies 19 identified in footnotes 261 to 266 of your 20 report indicate; correct? 21 A. That is correct. 22 Q. Okay. Are you aware of any other 23 studies that indicate BRCA2 genetic mutation is 24 associated with the development of mesothelioma 25 in the absence of asbestos exposure?	Page 29 1 A. No, not all those, right. Remember, 2 I said this was Colgate-Palmolive and Whittaker, 3 Clark & Daniels. 4 Q. Okay. All the materials you received 5 in the Sarah Plant and Shelby Payne cases came 6 from lawyers for Whittaker, Clark & Daniels, 7 Colgate, and Mennen? 8 A. If we're talking about materials, if 9 we're talking about the medical records and so 10 forth, then that's the, that's the way. 11 If we're talking about, like, 12 reliance materials, like articles and things, 13 then that's not the mechanism. 14 But if we're talking about, you know, 15 deposition transcripts, other legal materials, 16 and medical materials, then that's the way I got 17 them. 18 Q. From the lawyer? 19 A. From the lawyers. 20 Q. Did the lawyers for Whittaker, 21 Clark & Daniels, Mennen, or Colgate send you the 22 deposition transcript of Dr. Taylor Ripley? 23 A. I don't -- well, let me -- I don't 24 recall it, but let me just look at -- I have a 25 list here of what I received. I'll just

1 double-check. 2 So I don't -- I don't see it on my 3 list, and I don't recall receiving it. 4 Q. When you received the medical records 5 for Sarah Plant from the lawyers, did you review 6 them? 7 A. I did. 8 Q. Did you see what Miss Plant's 9 treating doctor said about whether or not her 10 BRCA2 genetic mutation caused her mesothelioma? 11 A. I saw two different things from 12 treating doctors, and I think they were 13 different treating doctors. So I don't -- I'd 14 have to go back and look to see, you know, which 15 doctor we're talking about. 16 I saw one that -- I'm just 17 paraphrasing -- who said that the BRCA2 probably 18 did not cause the mesothelioma. And then I saw 19 a different one -- and I don't know who's who -- 20 who actually was taking the BRCA2 defect into 21 account for the treatment plan because patients 22 with a BRCA2 defect with mesothelioma apparently 23 are more responsive to platinum-based therapies. 24 So I think one doctor acknowledged 25 its importance in the treatment plan and the	Page 30	1 you; correct? 2 A. It looks familiar. I mean, it's 3 literally what you have in front of you. I 4 could see if I could find a copy of this, if 5 this is that important. I think it looks, it 6 looks like what I've seen. 7 Q. You think the lawyers sent you a 8 forgery? 9 A. Oh, I don't. I don't. I'm just -- 10 the way you're asking the questions, though, 11 like you're asking me to just affirm something 12 about this document. And, you know, you're the 13 one that's showing it to me. So I think it's up 14 to you to affirm how you got it. 15 Q. See how it has Sarah J. Plant's name 16 on it and her date of birth? 17 A. I do. 18 Q. And then it says [as read]: She also 19 carries a BRCA2 genetic mutation. The 20 mesothelioma is probably not a consequence of 21 the genetic mutation. 22 Do you see that? 23 A. I do. 24 Q. And if you go to the next page of 25 Exhibit 3, it's signed by Laura Witherspoon, MD.	Page 32
1 other one said something like "probably didn't 2 cause it." 3 Q. Miss Plant had several treating 4 doctors? 5 A. Yes. 6 Q. Did any of them say BRCA2 caused her 7 mesothelioma? 8 A. I didn't see a statement like that. 9 ATTORNEY ADAMS: I'm going to attach 10 as Exhibit Number 3 an excerpt of a couple 11 medical records from Miss Plant's file. 12 (Exhibit 3 was marked for 13 identification.) 14 BY ATTORNEY ADAMS: 15 Q. Are you able to see what I've marked 16 as Exhibit 3, Doctor? 17 A. I do. 18 Q. This is a true and correct copy of 19 one of Sarah Plant's medical records; correct? 20 A. I mean, it's up to you decide. I 21 don't know. I mean, it looks like a good copy 22 of a record. But I have no idea how to know 23 that this is a true and correct copy. 24 Q. Okay. This is one that was sent to 25 you by the lawyers for the companies that hired	Page 31	1 Do you see that? 2 A. I do. 3 Q. That's one of Miss Plant's treating 4 physicians; correct? 5 A. It is. Is this the person that's 6 giving her counseling about like future 7 surgeries for -- you know, because of her BRCA2? 8 Maybe if I can see the top. I'm just 9 wondering -- when you say treating, I'm not sure 10 she was one of the ones who is treating her 11 cancer. 12 Yeah, no, okay. I was just trying to 13 figure out, you know, where this person is. So 14 this is the person who I think was advising her 15 about, you know, future risk of other cancers. 16 Q. Okay. But Dr. Witherspoon is a 17 doctor that Miss Plant went to and saw in person 18 for some kind of medical care; correct? 19 ATTORNEY LAWLER: Object to form. 20 THE WITNESS: That is correct. 21 BY ATTORNEY ADAMS: 22 Q. You have never been one of Sarah 23 Plant's treating physicians; correct? 24 A. That is correct. 25 Q. Miss Plant never came to you for	Page 33

Page 34 1 medical care; correct? 2 A. She has not. 3 Q. You've never met Miss Plant; correct? 4 A. I have not. 5 Q. You've never spoken to her; correct? 6 A. Correct. 7 Q. You wouldn't know what she looked 8 like if she bumped into you on the street; 9 correct? 10 A. I have not seen a picture of her. 11 Q. Do you agree or disagree with this 12 statement that Sarah Plant's mesothelioma is 13 probably not a consequence of her BRCA2 genetic 14 mutation? 15 ATTORNEY LAWLER: Object to form. 16 THE WITNESS: Yeah, I don't agree 17 with that statement. 18 BY ATTORNEY ADAMS: 19 Q. I'm just going to pages 4 and 5 of 20 Exhibit 3, which is the same statement. 21 [As read]: Also carries BRCA2 genetic mutation. 22 The mesothelioma is probably not a consequence 23 of the genetic mutation. 24 And this note is signed by another 25 one of Miss Plant's treating physicians. Do you	Page 36 1 ATTORNEY ADAMS: I'll mark as Exhibit 2 Number 4 the rough draft of the deposition 3 of Dr. Taylor Ripley. 4 (Exhibit 4 was marked for 5 identification.) 6 BY ATTORNEY ADAMS: 7 Q. Dr. Diette, are you able to see this 8 document where it says [as read]: Rough draft 9 only, deposition, Dr. Robert Ripley, January 27, 10 2023? 11 Do you see that? 12 A. I do. 13 Q. This is not a document you've seen 14 before; correct? 15 A. It does not look familiar. I don't 16 believe I've seen it. 17 Q. On page 219 of the document I asked 18 Dr. Ripley a few questions about the record that 19 I just showed you; okay? Can you assume that to 20 be true? 21 A. I'm sorry. I missed the first part 22 of what you said. 23 Q. I asked Dr. Ripley the same 24 questions – strike that. 25 I asked Dr. Ripley about the same
Page 35 1 see that? 2 A. Yeah, I think this is the same thing, 3 though. 4 ATTORNEY LAWLER: Object to form. 5 THE WITNESS: And it looks like a 6 copy-forward, you know, type of note. 7 It's signed by somebody else, but it looks 8 like it's from the same clinic. 9 BY ATTORNEY ADAMS: 10 Q. This note is signed by Sarah E. 11 Snell, MD. Do you see that? 12 A. I do. 13 Q. Okay. I presume you disagree with 14 this statement – never mind, I'll just withdraw 15 it. 16 We have two of Miss Plant's treating 17 physicians signing separate documents indicating 18 her mesothelioma was probably not a consequence 19 of her BRCA2 genetic mutation; correct? 20 ATTORNEY LAWLER: Object to form. 21 THE WITNESS: That is correct. 22 BY ATTORNEY ADAMS: 23 Q. I'm sorry. I didn't hear your 24 answer. 25 A. Oh, I said "That is correct."	Page 37 1 document I just showed you here at page 219; 2 okay? You with me? 3 A. I am. Thank you. 4 Q. And my question is [as read]: 5 It says, quote, the mesothelioma is 6 probably not a consequence of the genetic 7 mutation? Do you see that? 8 Answer: Yeah. I agree with him on 9 that. 10 Question: How come? 11 Because BRCA2 doesn't cause 12 mesothelioma. It makes her at risk of not 13 repairing injuries as well as a patient 14 should because it's, it's a mutation in a 15 DNA repair gene, and so – but it's not a 16 causative event. It's, it's a lack of 17 recovery event, if you will. 18 Do you see that testimony from 19 Dr. Ripley? 20 A. I do. 21 Q. Okay. Do you agree or disagree with 22 Dr. Ripley's testimony? 23 ATTORNEY LAWLER: Object to form. 24 THE WITNESS: I agree. This is 25 exactly what I was telling you earlier,

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Page 38 1 right. This is why I said it was 2 naturally occurring, because I don't, I 3 don't know that there's enough information 4 to say this gene literally causes cancer, 5 but it contributes to the development of 6 it or the perpetuation of it because it 7 can't fix an error. 8 So this fits with exactly what I was 9 saying earlier. 10 BY ATTORNEY ADAMS: 11 Q. Okay. What about the part where he 12 says [as read]: I agree with the treating 13 doctors that the mesothelioma is probably not a 14 consequence of the genetic mutation? 15 Do you agree with that or not? 16 A. I think his answer's inconsistent 17 with that statement above it because, because he 18 goes to say it's not a consequence – 19 "consequence" is a different word than 20 "cause" – but he also says that it's a repair 21 gene. So it's not a causative event; it's a 22 lack of recovery event, right. 23 But that's still an event, right. 24 It's still something that matters. So I think 25 his answer is inconsistent with the statement	Page 40 1 Do you see the portion that I've 2 read? 3 A. I do. 4 Q. Do you agree with Dr. Ripley's 5 agreement or do you disagree? 6 ATTORNEY LAWLER: Object to form. 7 THE WITNESS: It's impossible for me 8 to agree with his agreement. I mean, he's 9 himself, I'm not him. I could agree with 10 you that that's what he stated. 11 I just think that his fuller answer 12 down below after the "how come" actually 13 is a better explanation of what he's 14 talking about. And he's saying that the 15 BRCA gene doesn't cause it, but he talks 16 about how it contributes to the cancer. 17 BY ATTORNEY ADAMS: 18 Q. Three separate treating doctors for 19 Sarah Plant have indicated that her BRCA2 20 genetic defect – genetic mutation, excuse me – 21 is probably not – strike that. Let me start 22 over. 23 Three separate treating doctors for 24 Sarah Plant have indicated that her mesothelioma 25 is probably not a consequence of her BRCA2
Page 39 1 that he was read that he, you know, didn't make 2 to begin with. 3 Q. So you disagree with Dr. Ripley's 4 agreement that the mesothelioma is probably not 5 a consequence of the genetic mutation? 6 ATTORNEY LAWLER: Object to form. 7 THE WITNESS: It looks to me as if he 8 clarified it by saying it doesn't cause it 9 but then he explained what the role was. 10 So I think he answered the question. But 11 I don't think it's – I think he qualified 12 it in a way that makes a lot of sense. 13 BY ATTORNEY ADAMS: 14 Q. Let's just isolate the part where 15 Dr. Ripley says [as read]: Yeah, I agree with 16 them on that. 17 Right? You know what I'm talking 18 about? 19 A. I do. 20 Q. Lines 3 to 5 [as read]: 21 Question: It says, quote, 22 mesothelioma is probably not a consequence 23 of a genetic mutation. 24 Do you see that? 25 Yeah. I agree with him on that.	Page 41 1 genetic mutation; correct? 2 ATTORNEY LAWLER: Objection; 3 mischaracterizes, assumes facts. 4 THE WITNESS: So I think literally – 5 you know, we saw those two articles or, I 6 mean, those two abstractions from the 7 medical records where they signed the same 8 statement. And I see that he says that he 9 agrees here in this third case. But I 10 think his full answer is not fully 11 consistent with that because he actually 12 describes why it is a consequence. 13 ATTORNEY ADAMS: Move to strike the 14 nonresponsive. 15 BY ATTORNEY ADAMS: 16 Q. Do you agree that three separate 17 treating physicians for Sarah Plant have 18 indicated her mesothelioma is probably not a 19 consequence of her BRCA2 genetic mutation or do 20 you disagree? 21 A. I'm not going to – 22 ATTORNEY LAWLER: Objection; 23 mischaracterizes, assumes facts. 24 THE WITNESS: I'm not going to answer 25 differently than I did because I think my

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Page 42 1 answer is the correct answer. 2 BY ATTORNEY ADAMS: 3 Q. I'm asking you a new question, now. 4 A. No, it sounds like the same question 5 to me. And if there's a difference, I can't 6 detect what it is. 7 Q. Do you agree that three separate 8 treating physicians for Sarah Plant -- 9 Dr. Witherspoon, Dr. Snell, and Dr. Ripley -- 10 have all stated that her mesothelioma is 11 probably not a consequence of her BRCA2 genetic 12 mutation? Do you agree or disagree? 13 ATTORNEY LAWLER: Objection; 14 cumulative, mischaracterizes, and assumes 15 facts. 16 THE WITNESS: And I disagree for the 17 reasons I said, right. If you were going 18 to just try to trick me and just show me 19 that first little snippet of the answer, 20 then it would be hard to disagree with. 21 But when you see what his actual full 22 answer is, then that's not consistent with 23 him agreeing that it's not a consequence. 24 BY ATTORNEY ADAMS: 25 Q. So when Dr. Ripley said -- was	Page 44 1 event. So that part I agree with. 2 BY ATTORNEY ADAMS: 3 Q. Do you agree with Dr. Ripley's 4 testimony that BRCA2 doesn't cause mesothelioma? 5 ATTORNEY LAWLER: Object to form. 6 THE WITNESS: So I think the answer 7 is I don't know, because I haven't seen 8 studies that tell whether or not these 9 germline mutations that are linked to 10 mesothelioma, whether they can, all by 11 themselves, cause a cancer or whether they 12 are just simply in the role of not 13 repairing a defect that come from some 14 other mechanism. 15 So I think there's enough information 16 to say that BRCA2 can't cause a tumor. 17 But I haven't seen affirmative evidence 18 that shows that it does. 19 BY ATTORNEY ADAMS: 20 Q. Does BRCA2 -- okay. You haven't seen 21 evidence that -- strike that. 22 Have you seen evidence that BRCA2 23 causes genetic mutation? 24 A. The BRCA2 is a genetic mutation. And 25 the thing we're talking about, right, I
Page 43 1 asked -- [as read]: It says, quote, the 2 mesothelioma was probably not a consequence of 3 the genetic mutation. Do you see that? And he 4 answered, Yeah, I agree with him on that -- he 5 didn't say the mesothelioma is probably not a 6 consequence of the genetic mutation? 7 Is that your testimony? 8 ATTORNEY LAWLER: Object to form; 9 argumentative. 10 THE WITNESS: I see it exactly. But 11 I think -- I don't know if you're not 12 listen carefully. But I think since he 13 gave a fuller answer after he said "how 14 come," that that is inconsistent with it 15 not being a consequence of the genetic 16 mutation. 17 BY ATTORNEY ADAMS: 18 Q. Okay. So you agree with Dr. Ripley? 19 ATTORNEY LAWLER: Object to form. 20 THE WITNESS: I agree with this 21 statement that we see where he explains 22 that the BRCA2 didn't cause the 23 mesothelioma, per se, but that because 24 it's the mutational -- it's a repair gene 25 for mutation, it's a lack-of-recovery	Page 45 1 assume -- we're talking about a mutation in the 2 BRCA2 gene. 3 ATTORNEY ADAMS: Move to strike as 4 nonresponsive. 5 BY ATTORNEY ADAMS: 6 Q. Have you seen an indication that 7 BRCA2 causes genetic mutation? 8 ATTORNEY LAWLER: Object to form. 9 THE WITNESS: So it itself is -- 10 we're referring to a genetic mutation. 11 It's a shorthand for a genetic mutation in 12 a particular gene. 13 I have not seen that that particular 14 abnormal gene can itself induce a genetic 15 defect in another cell. But I don't know 16 that it can't. I just haven't seen that 17 it can. 18 BY ATTORNEY ADAMS: 19 Q. Have you seen evidence that BRCA2 can 20 cause a genetic defect in mesothelial cells? 21 ATTORNEY LAWLER: Object to form. 22 THE WITNESS: I haven't seen anything 23 on that one way or the other. 24 BY ATTORNEY ADAMS: 25 Q. In your report you say [as read]: In

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Page 46 1 women in the US, most cases of mesothelioma, 2 77 percent, are not caused by asbestos exposure. 3 Do I have that right? 4 A. You do. 5 Q. What's the source of that statement? 6 Is there a way for you to point me to it in your 7 report or some other way? 8 A. So the general statement comes from 9 multiple sources. But the specific 77 percent 10 comes from, as you know, from Spirtas from 1994. 11 Q. Can you identify any study, 12 publication, or literature written by someone 13 who was not paid by talc defendants, asbestos 14 defendants, or their lawyers that says over 15 70 percent of women's mesotheliomas are not 16 caused by asbestos? 17 ATTORNEY LAWLER: Object to form. 18 THE WITNESS: So we're talking about 19 attributable risk. And that's the only 20 paper I can find -- or most recent paper 21 in the United States -- that has that 22 attributable risk estimate. And as far as 23 I know, the authors of that paper were not 24 paid by any of the types of, you know, 25 entities that you just listed.	Page 48 1 Q. First of all, do you know how to 2 spell -- is it H-E-N-L-A-Y or E-Y? 3 A. E-Y. It's listed on page 61 of my 4 report. 5 Q. Thank you. So I've got Spirtas 1994, 6 Henley, Moolgavkar, Price and Ware. 7 Are there any other studies or 8 authors you can identify in support of your 9 opinion that most mesotheliomas in women are 10 because -- are not caused by asbestos exposure? 11 A. I'd have to look back. I've seen it 12 written off in -- I think there's one of the 13 papers where, like from a mesothelioma group 14 that Carbone is part of. I think there was like 15 a 2020 or 2019 paper. I haven't memorized it. 16 I think they have a statement in there about 17 that. But the foundation for it comes from the 18 epidemiology studies. 19 And the Moolgavkar, there's more than 20 one. There's a book chapter as well as a paper. 21 And Price and Ware, there's more than one, you 22 know, more than one publication. 23 Q. Moolgavkar you know has been 24 routinely hired and paid by asbestos companies 25 and talc companies; correct?
Page 47 1 BY ATTORNEY ADAMS: 2 Q. You're talking about Spirtas 1994? 3 A. I am. 4 Q. What are the other sources for your 5 77 percent spontaneous opinion? 6 A. So what I tried to clarify is that 7 the general statement that most women's 8 mesotheliomas in the US are not caused by 9 asbestos comes from a different body of evidence 10 as well. 11 So the 77 percent specifically only 12 links to Spirtas, right. That specific number 13 only links to Spirtas. 14 The other comes from other 15 epidemiologic studies. So, for example, you 16 know, from Henley, from Moolgavkar, from Price 17 and Ware, that have looked at the historic 18 trends through the SEER data and looking at the, 19 essentially, you know, flat or unfluctuating 20 rate of mesothelioma among women and then the 21 lack of an association with historic asbestos 22 usage in the United States. 23 Q. Can you give me a more precise cite 24 on the Henley paper? 25 A. Let's see.	Page 49 1 ATTORNEY LAWLER: Object to form. 2 THE WITNESS: I know nothing about 3 routinely. I'm aware of at least one 4 case, I think, that he was involved in 5 that I was involved in. But otherwise, I 6 don't know what is -- you know, how he 7 spends his time. 8 BY ATTORNEY ADAMS: 9 Q. You didn't know that the asbestos 10 brake companies hire them all the time to defend 11 them in asbestos cases? 12 ATTORNEY LAWLER: Object to form. 13 THE WITNESS: Yeah, I have no idea if 14 that's true or not. 15 BY ATTORNEY ADAMS: 16 Q. And you know that Bertram Price has 17 been paid by the law firms that represent the 18 talc companies in asbestos litigation; correct? 19 A. I have -- 20 ATTORNEY LAWLER: Object to form. 21 THE WITNESS: Yeah, I have no 22 information about that. 23 BY ATTORNEY ADAMS: 24 Q. You know that Carbone has been 25 retained and paid by talc companies in asbestos

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1 litigation; correct? 2 ATTORNEY LAWLER: Object to form. 3 THE WITNESS: I think -- I don't have 4 knowledge of that other than I think I saw 5 a disclosure where he's been retained by 6 plaintiffs and defendants, I think, in 7 either talc- or asbestos-related cases, if 8 I remember right. But otherwise, I don't 9 have knowledge about that. 10 BY ATTORNEY ADAMS: 11 Q. He's been retained by plaintiffs, you 12 think? 13 A. I think -- if I remember right, I 14 think I saw a disclosure statement in one of his 15 papers. 16 And actually -- so if we're talking 17 about retained by, that seems like a technical 18 term. Like maybe he did some work for a 19 plaintiff that isn't the same as being retained 20 by; or maybe he read a study or a slide or 21 something. I don't know. But I did see 22 something that it wasn't just defense work. 23 Q. Do you know whether or not Henley has 24 been retained or paid by asbestos companies, 25 talc companies, or their lawyers?	Page 50 1 Q. Okay. So you don't know whether or 2 not the authors who you have relied on to 3 support your opinion that most mesotheliomas in 4 women are not related to asbestos have been paid 5 by talc companies, asbestos companies, or their 6 lawyers? 7 ATTORNEY LAWLER: Object to form. 8 THE WITNESS: Yeah, I can't, I can't 9 answer that. 10 BY ATTORNEY ADAMS: 11 Q. In your report in the Payne case, 12 which I marked as Exhibit 2, you indicate that 13 [as read]: There is no clinical evidence that 14 Miss Payne had any exposure to asbestos from 15 Avon, Mennen, or Cashmere Bouquet cosmetic 16 talcum powders. 17 Correct? 18 A. That sounds right. I'm just opening 19 to the -- you looking in the assessment? 20 Q. I think it was the conclusions at the 21 end. I can pull it up if you need it. 22 A. No, okay, I see it. It's probably in 23 both. It's for sure in the conclusions. I see 24 it. 25 Q. Did you look at any materials from
Page 51 1 ATTORNEY LAWLER: Object to form. 2 THE WITNESS: I have no idea. I 3 think it wouldn't have been possible at 4 the time that the paper came out because 5 that was a, like a CDC paper. I would 6 imagine they, you know, wouldn't be 7 involved in litigation. 8 BY ATTORNEY ADAMS: 9 Q. Can you identify any author of any 10 paper or study who you know has not been paid by 11 talc, asbestos -- talc companies, asbestos 12 companies, or their lawyers who says that most 13 mesotheliomas in women are not related to 14 asbestos? 15 ATTORNEY LAWLER: Object to form. 16 THE WITNESS: I need some time to 17 pull out the paper that Carbone's on. But 18 that was quite a long panel of -- quite a 19 long, long list of authors. 20 But I also -- I don't have like a 21 registry of who's done work for whom under 22 what circumstances. So it's kind of an 23 impossible question for me to ask -- 24 answer, I mean. 25 BY ATTORNEY ADAMS:	Page 53 1 Avon before reaching that conclusion? 2 A. I guess I don't know what you mean by 3 "from Avon." You mean specifically from the 4 company? 5 Q. Yeah; like company documents, 6 testing, anything like that. 7 A. I have not. 8 Q. Did you look at any Mennen corporate 9 documents before reaching your opinion that 10 Miss Payne was not exposed to asbestos from any 11 Mennen talcum product? 12 ATTORNEY LAWLER: Object to form. 13 THE WITNESS: I have not. 14 BY ATTORNEY ADAMS: 15 Q. Did you look at any Colgate internal 16 corporate documents before reaching your 17 conclusion that Miss Payne was not exposed to 18 asbestos from any Colgate talcum powders? 19 ATTORNEY LAWLER: Object to form. 20 THE WITNESS: I have not. 21 BY ATTORNEY ADAMS: 22 Q. Are you aware that there's a -- 23 strike that. 24 What is the Avon product that 25 Miss Payne used? You know how they have names

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Page 54 1 like Skin So Soft, Wild Rose, Unforgettable, 2 stuff like that? 3 A. Yeah. I think Cotillion, I think 4 Cotillion was the, like, body powder, was the 5 one that was identified. 6 Q. Did the lawyers for Avon give you any 7 of the testing they have for asbestos in their 8 Cotillion powder? 9 ATTORNEY IULO: Objection. 10 ATTORNEY LAWLER: Object to form. 11 THE WITNESS: They had not. 12 BY ATTORNEY ADAMS: 13 Q. Okay. Did you assume that there was 14 no asbestos in Avon's Cotillion powder at any 15 time? 16 ATTORNEY IULO: Objection; form. 17 THE WITNESS: I did not. 18 BY ATTORNEY ADAMS: 19 Q. How did you reach the opinion that 20 Miss Payne was never exposed to any asbestos 21 from any Avon Cotillion talcum powder? 22 A. I didn't. So the statement you read 23 is that there's no clinical evidence that she 24 had exposure, which is not the same as saying 25 she never had any exposure.	Page 56 1 A. I have no idea what you're talking 2 about. 3 (Exhibit 5 was marked for 4 identification.) 5 BY ATTORNEY ADAMS: 6 Q. I've marked as Exhibit 5 the report 7 of Lee Poye dated July 12, 2029. 8 A. 2029? Is this a future report from 9 six years from now? 10 Q. 2019; sorry. Are you able to see 11 that? 12 A. I can see that. 13 Q. See how it says July 12, 2019? 14 A. I do. 15 Q. And then it says [as read]: Analysis 16 of Cashmere Bouquet and Avon Cotillion cosmetic 17 talc products for the presence of asbestos. 18 Do you see that up at the top, 19 bolded? 20 A. I do. 21 Q. And then on the second page it says 22 Summary of Analytical Results. And it's signed 23 by Lee W. Poye, vice president, J3 Resources, 24 Inc. 25 Do you see that?
Page 55 1 Q. What does "clinical evidence" mean? 2 A. Looking for things through the 3 medical records that would establish that. 4 Q. Okay. So in Miss Payne's medical 5 records there's no evidence of exposure to 6 asbestos from Avon Cotillion powder; that's your 7 opinion? 8 A. It is my opinion. 9 Q. Okay. Are you aware that Avon's own 10 expert found 1 percent anthophyllite asbestos in 11 Cotillion talcum powder? 12 ATTORNEY IULO: Objection. 13 THE WITNESS: I'm not aware of that. 14 I don't know if that's right or not. I 15 don't have any way to corroborate that. 16 BY ATTORNEY ADAMS: 17 Q. Well, you could read the study; 18 right? 19 A. What's the study? 20 Q. The study that Avon's expert 21 performed on Avon Cotillion cosmetic talc 22 products for asbestos. 23 ATTORNEY IULO: Objection to form. 24 BY ATTORNEY ADAMS: 25 Q. Do you know what I'm talking about?	Page 57 1 A. I do. 2 Q. It says [as read]: Polarized light 3 microscopy, ISO 22262-1, found the samples 4 contained approximately 94 percent to a hundred 5 percent talc. Platy talc, fibrous talc, and/or 6 talc ribbons was observed and documented in all 7 five samples. 1 percent anthophyllite asbestos 8 was detected in sample AV-4. 9 Do you see that? 10 A. I do. 11 Q. Do you have any information to 12 dispute Mr. Poye's findings? 13 ATTORNEY LAWLER: Object to form. 14 ATTORNEY IULO: Objection. 15 THE WITNESS: This isn't my 16 expertise. I mean, I'm not an expert in 17 the same field he is. So I can't critique 18 his findings one way or the other. 19 BY ATTORNEY ADAMS: 20 Q. [As read]: Analytical transmission 21 electron microscopy, ISO 22262-2, following 22 heavy liquid separation identified 23 0.00256 percent tremolite asbestos in AV-2 and 24 0.330 percent anthophyllite asbestos in sample 25 AV-4.

1 Do you see that? 2 A. I do. 3 Q. And then if you go to the next page, 4 it's got pictures of the four Avon Cotillion 5 samples that Mr. Poye tested. Do you see that? 6 A. I see five pictures. I don't know. 7 Q. One's Cashmere Bouquet. See the 8 other four are Avon Cotillion? 9 A. I see that now; yeah. 10 Q. And so if this report is true, then 11 Mr. Poye found up to 1 percent asbestos in the 12 very Avon powder that Miss Payne used for years; 13 correct? 14 ATTORNEY IULO: Objection. 15 ATTORNEY LAWLER: Object to form. 16 THE WITNESS: I don't, I don't know 17 what the sources of these are. 18 BY ATTORNEY ADAMS: 19 Q. The Avon lawyers never showed you 20 this report? 21 ATTORNEY IULO: Objection. 22 THE WITNESS: We've already discussed 23 that. No, I've not seen this. 24 BY ATTORNEY ADAMS: 25 Q. Is there still no clinical evidence	Page 58	1 ATTORNEY ADAMS: And I'm going to 2 start with Plant. I'll attach as 3 Exhibit 6 notes regarding Eric Johnson in 4 the Plant case. 5 (Exhibit 6 was marked for 6 identification.) 7 ATTORNEY ADAMS: I'll attach as 8 Exhibit 7 notes regarding Dr. Maddox in 9 the Plant case. 10 (Exhibit 7 was marked for 11 identification.) 12 THE WITNESS: Pardon me just for 13 interrupting. Are you asking me to 14 confirm that these are what I have, or are 15 you just reading them? 16 BY ATTORNEY ADAMS: 17 Q. I'm hoping that once I get through 18 reading them, you can answer a question like: 19 Do I have all of the materials you've generated 20 in the Sarah Plant case? 21 A. Sure. So I might just need a moment 22 to pull up my list, then, so I can, you know, 23 mentally go through it and see if you're reading 24 everything that I know of too. 25 Q. Right. Let me know when you've done	Page 60
1 that Miss Payne had any exposure to asbestos 2 from Avon cosmetic talcum powders? 3 A. That's still correct. 4 Q. But clinical evidence doesn't mean 5 all evidence; right? It just means medical 6 records? 7 ATTORNEY LAWLER: Objection. 8 ATTORNEY IULO: Objection. 9 THE WITNESS: That's what I, that's 10 what I intend it to mean. 11 BY ATTORNEY ADAMS: 12 Q. Another opinion you put in your 13 report about Miss Payne is that [as read]: Her 14 personal and family history of neoplasms, it is 15 possible that Miss Payne had a hereditary risk 16 for developing cancer. 17 Correct? 18 A. That's correct. 19 Q. Can you go further than "possible"? 20 A. I cannot. 21 ATTORNEY ADAMS: I want to attach the 22 documents quickly that we received in the 23 Payne and Plant cases and make sure I have 24 everything; okay? 25 THE WITNESS: Sure thing.	Page 59	1 that. 2 A. Okay. I'm all set. 3 ATTORNEY ADAMS: Okay. So I attached 4 as Exhibit 6 your notes regarding Eric 5 Johnson's deposition in the Plant case. 6 Exhibit 7 will be Dr. Diette's notes 7 regarding Dr. Maddox in the Plant case. 8 Exhibit 8 will be Dr. Diette's notes 9 regarding Patrice Johnson in the Plant 10 case. 11 (Exhibit 8 was marked for 12 identification.) 13 ATTORNEY ADAMS: Exhibit 9 will be 14 Dr. Diette's notes regarding Sarah Plant's 15 deposition in the Plant case. 16 (Exhibit 9 was marked for 17 identification.) 18 ATTORNEY ADAMS: Exhibit 10 will be 19 Dr. Diette's document regarding Sarah 20 Plant, legal and employment notes. 21 (Exhibit 10 was marked for 22 identification.) 23 ATTORNEY ADAMS: Exhibit 11 will be 24 Dr. Diette's medical notes in the Plant 25 case.	Page 61

Page 62 1 (Exhibit 11 was marked for 2 identification.) 3 ATTORNEY ADAMS: Exhibit 12 be 4 Dr. Diette's pulmonary function test 5 summary chart in the Plant case. 6 (Exhibit 12 was marked for 7 identification.) 8 ATTORNEY ADAMS: Exhibit 13 will be 9 Dr. Diette's CV in the Plant case. 10 (Exhibit 13 was marked for 11 identification.) 12 BY ATTORNEY ADAMS: 13 Q. How do I tell if it's your most 14 current CV, Dr. Diette? Is there an easy way? 15 A. No. It just is. I mean it's -- 16 that's the one that I, you know, I sent along to 17 my assistant. 18 ATTORNEY ADAMS: Okay. Exhibit 14 19 will be Dr. Diette's testimony list that 20 was produced in the Plant case. 21 (Exhibit 14 was marked for 22 identification.) 23 ATTORNEY ADAMS: Exhibit 15 will be 24 Dr. Diette's fee schedule that was 25 produced in the Plant case.	Page 64 1 Q. Right. 2 A. You didn't say the transcripts, but I 3 have the transcript. But I didn't probably 4 produce it, if that's right word, because I 5 assumed you have that, like you have the same 6 thing I do. 7 Q. Right, okay. Have I attached all of 8 the documents you generated, you created in the 9 Sarah Plant case? 10 A. Yes. And it includes my report as 11 well. 12 Q. Okay. Were there other materials you 13 received but did not summarize? 14 Understand? In other words, I know 15 you receive the deposition of Eric Johnson 16 because you summarized it. My question is: 17 Were there some depositions or materials that 18 you received that you didn't identify in the 19 summary? 20 A. Well, I get, like, the reports, like 21 the expert reports. I didn't, I didn't create a 22 summary of those, although I included a little 23 bit of, you know, text in my report to 24 acknowledge, you know, what they had put in the 25 report.
Page 63 1 (Exhibit 15 was marked for 2 identification.) 3 ATTORNEY ADAMS: Exhibit 16 will be 4 Dr. Diette's invoices from the Plant case. 5 (Exhibit 16 was marked for 6 identification.) 7 BY ATTORNEY ADAMS: 8 Q. Exhibit 17 will be -- now we're going 9 to start on the Payne documents. I don't know 10 if you need -- why don't we pause here. 11 A. Yeah. 12 Q. Have I now attached all of the 13 documents you have produced in the Sarah Plant 14 case? 15 A. Just -- I'm just stumbling on 16 "produced" because my case materials also 17 include the actual documents themselves, right. 18 So like the medical records and so forth as an 19 example. So you're trying to not exclude, like, 20 the primary source documents or...? 21 Q. Well, we didn't get those. But I 22 assumed you had them because of the summaries. 23 A. Well, I'll give you another example. 24 Like where there's a deposition, I have the 25 deposition transcript.	Page 65 1 Q. Okay. Anything else? 2 A. No. So that would be like -- you'd 3 find that in my report, like whatever my 4 abstraction is from those. 5 Q. Yeah, I saw that. Okay. Is there 6 any other materials received in this case that 7 you haven't identified in your report or 8 summarized in some other document? 9 A. No, nothing else. 10 ATTORNEY ADAMS: All right. I'll 11 attach as Exhibit 17 Dr. Diette's medical 12 notes in the Payne case. 13 (Exhibit 17 was marked for 14 identification.) 15 THE WITNESS: Okay. 16 ATTORNEY ADAMS: Exhibit 18 will be 17 Dr. Diette's notes in the Payne case. 18 (Exhibit 18 was marked for 19 identification.) 20 ATTORNEY ADAMS: Exhibit 19 will be 21 Dr. Diette's notes regarding the 22 deposition of Shannon Payne Lancaster in 23 the Payne case. 24 (Exhibit 19 was marked for 25 identification.)

1 ATTORNEY ADAMS: Exhibit 20 will be 2 Dr. Diette's notes regarding the 3 deposition of Kelly Payne Clark in the 4 Payne case. 5 (Exhibit 20 was marked for 6 identification.) 7 ATTORNEY ADAMS: Exhibit 21 will be 8 Dr. Diette's pulmonary function test 9 results, summary chart, in the Payne case. 10 (Exhibit 21 was marked for 11 identification.) 12 ATTORNEY ADAMS: Exhibit 22 will be 13 Dr. Diette's invoices in the Payne case. 14 (Exhibit 22 was marked for 15 identification.) 16 BY ATTORNEY ADAMS: 17 Q. Okay. Have I attached all of the 18 documents you have created in the Payne case, 19 Dr. Diette? 20 A. Plus my report. 21 Q. Which I attached earlier but... 22 A. Yes. 23 Q. Okay. Are there any documents you 24 received in the Payne case that you did not 25 identify in your report or summarize in some	Page 66	1 mean, I think I've just seen papers from, 2 you know, plaintiff's experts who have 3 published some of the results. 4 BY ATTORNEY ADAMS: 5 Q. Okay. Is crocidolite a type of 6 asbestos that you have seen found in talc? 7 A. I've not seen that. 8 Q. How about amosite? 9 ATTORNEY LAWLER: Object to form. 10 THE WITNESS: Yeah, no, I've not seen 11 that. 12 BY ATTORNEY ADAMS: 13 Q. Okay. Is tremolite a type of 14 asbestos that you have seen found in talc? 15 ATTORNEY LAWLER: Object to form. 16 THE WITNESS: Yeah, I've seen it 17 reported in different ways, you know, 18 through the plaintiff's experts, 19 essentially. 20 BY ATTORNEY ADAMS: 21 Q. Have you seen anthophyllite reported 22 as a type of asbestos found in talc? 23 ATTORNEY LAWLER: Object to form. 24 THE WITNESS: Yes; in the same way, 25 same way I've seen that.	Page 68
1 other document? 2 A. No. 3 ATTORNEY ADAMS: I'm going to attach 4 just for the record as Exhibit 23 the 5 notice of deposition in the Plant case. 6 And Exhibit 24 will be the notice of 7 deposition in the Payne case. 8 (Exhibit 23 was marked for 9 identification.) 10 (Exhibit 24 was marked for 11 identification.) 12 BY ATTORNEY ADAMS: 13 Q. Dr. Diette, do you have an 14 understanding of what types of asbestos can be 15 found in certain -- in talc, just in general? 16 A. I have an understanding of what's 17 been alleged in some of these cases. 18 Q. What about what you've seen as far as 19 the literature about the types of asbestos found 20 in talc? Do you have any understanding of what 21 types of asbestos are found in certain types of 22 talc? 23 ATTORNEY LAWLER: Object to form. 24 THE WITNESS: I think what I've seen 25 overlaps entirely with the litigation. I	Page 67	1 BY ATTORNEY ADAMS: 2 Q. How about actinolite? 3 ATTORNEY LAWLER: Object to form. 4 THE WITNESS: I don't recall seeing 5 actinolite. 6 BY ATTORNEY ADAMS: 7 Q. How about chrysotile? 8 ATTORNEY LAWLER: Object to form. 9 THE WITNESS: I do recall seeing 10 chrysotile. 11 BY ATTORNEY ADAMS: 12 Q. Okay. So the types of asbestos 13 you've seen reported through plaintiffs or their 14 experts as being found in certain types of talc 15 are tremolite, anthophyllite, and chrysotile? 16 ATTORNEY LAWLER: Object to form. 17 THE WITNESS: That's right. 18 BY ATTORNEY ADAMS: 19 Q. Have you seen anyone other than 20 plaintiffs or their experts report finding 21 tremolite, anthophyllite, or chrysotile in talc? 22 ATTORNEY LAWLER: Objection. 23 THE WITNESS: And we're talking about 24 asbestos in each of those cases, right, as 25 opposed to, like, anthophyllite that's not	Page 69

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Page 70 1 asbestos, or tremolite? 2 BY ATTORNEY ADAMS: 3 Q. Let's start with -- I'll ask a more 4 precise question. 5 Have you seen anyone other than 6 plaintiffs or their experts report finding 7 tremolite asbestos, anthophyllite asbestos, or 8 chrysotile in talc? 9 ATTORNEY LAWLER: Objection. 10 THE WITNESS: So I think I saw -- in 11 Mr. Seagrave's report I saw identification 12 of -- I don't remember -- I think I saw 13 anthophyllite asbestos identified in one 14 example, or maybe more than one sample. 15 I don't know if he identified any of 16 those other ones we just talked about. 17 And I may have seen others, but I don't 18 recall them right now, about, you know, 19 other people finding them. 20 BY ATTORNEY ADAMS: 21 Q. Your understanding is Mr. Seagrave is 22 a defense expert in the Payne and Plant case -- 23 cases? 24 ATTORNEY LAWLER: Objection. 25 THE WITNESS: It -- that's my	Page 72 1 Mr. Poye. I don't know if that's the type 2 of document you're talking about, if 3 that's an internal document. 4 BY ATTORNEY ADAMS: 5 Q. No. I'm talking about something 6 different, like internal corporate records from 7 the 1970s, for example, in Avon finding 8 tremolite in talc. 9 ATTORNEY IULO: Objection to form. 10 BY ATTORNEY ADAMS: 11 Q. Have you seen anything like that? 12 A. So it's possible in deposition or 13 trial somebody might have shown me something 14 that that. But otherwise the answer's no. 15 Q. What are the asbestos-related 16 diseases? 17 A. There are several. There is, you 18 know, mesothelioma, lung cancer, laryngeal 19 cancer, asbestosis. There are -- it's not 20 really disease, but pleural plaques are a 21 finding. Diffuse pleural thickening is a 22 finding not necessarily a disease. There's 23 rounded atelectasis, which is a finding from 24 asbestos exposure, which I wouldn't call a 25 disease. And then there's also a benign pleural
Page 71 1 understanding. 2 BY ATTORNEY ADAMS: 3 Q. Have you seen anyone other -- strike 4 that -- anyone else other than Mr. Seagrave who 5 is not a plaintiff or plaintiff's expert? 6 A. It's possible I have, but I don't 7 recall any at this point. 8 Q. Okay. Have you seen anyone finding 9 tremolite, anthophyllite, or chrysotile in talc 10 who is not a plaintiff or plaintiff's expert? 11 ATTORNEY LAWLER: Object to form. 12 THE WITNESS: I don't know how that's 13 different than what you asked me already. 14 BY ATTORNEY ADAMS: 15 Q. I took out the word "asbestos." 16 A. Oh, I see. So -- no. No, I'm not -- 17 like the non-asbestos forms, I haven't. 18 Q. Have you seen any of Avon's internal 19 corporate records finding tremolite and 20 anthophyllite in talc? 21 ATTORNEY IULO: Objection. 22 THE WITNESS: I haven't received any. 23 I can't recall if I've ever been shown, 24 you know, a document like -- for example, 25 you showed me a document before from	Page 73 1 effusion, which I guess might count as a 2 disease. 3 Q. Does being diagnosed with an 4 asbestos-related disease indicate someone was 5 likely exposed to asbestos? 6 ATTORNEY LAWLER: Object to form. 7 THE WITNESS: It depends on what 8 you're talking about. If somebody's 9 diagnosed with asbestosis, you know, and 10 it's literally asbestosis and that's, you 11 know, not contested, right, everyone 12 agrees it's asbestosis, the exposure is 13 baked into the name of that, that 14 particular disorder. 15 But otherwise, the other ones don't 16 imply that with such absolute, you know, 17 certainty, the way that asbestosis would. 18 BY ATTORNEY ADAMS: 19 Q. Do you agree that there are four 20 different regions where mesothelioma can 21 develop? 22 A. And we're talking about in the human 23 body? 24 Q. Correct. 25 A. So pleural, peritoneal, pericardial

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Page 74 1 and tunica vaginalis; yeah. 2 Q. Okay. Which one of those four types 3 of mesothelioma is most strongly associated with 4 asbestos exposure? 5 A. The pleural form. 6 Q. That's the form that both Sarah 7 Payne -- excuse me. That's the form that both 8 Sarah Plant and Shelby Payne have; correct? 9 A. That is correct. 10 Q. Does Shelby Payne have any genetic 11 mutations that you can identify with a 12 reasonable degree of medical certainty that 13 contributed to her development of mesothelioma? 14 A. So what I've seen, she's not had, you 15 know, genetic germline testing. So there's no 16 way for me to say that she does have such a 17 defect. 18 Q. Have either Sarah Plant or Shelby 19 Payne had a tissue digestion performed? 20 A. If they have, I haven't seen it. 21 Q. Have you ever performed a tissue 22 digestion? 23 A. I have not. 24 Q. Have you ever performed a fiber 25 burden analysis?	Page 76 1 career? 2 A. I wouldn't agree to that because it's 3 a really rough estimate. But it's -- I would 4 say it's somewhere in the tens. It's certainly 5 not zero, and I don't think would be a hundred. 6 Yes, it's somewhere in the tens. 7 Q. It's certainly not anywhere near 8 to 300; correct? 9 A. I -- 10 Q. Let me ask a better question. You 11 have not seen anywhere near 300 patients with 12 mesothelioma in your career; correct. 13 ATTORNEY LAWLER: Object to form. 14 THE WITNESS: Yeah, it can't be 300. 15 BY ATTORNEY ADAMS: 16 Q. Okay. Are you the director of any 17 mesothelioma groups? 18 A. I am not. 19 Q. Are you the director of any 20 mesothelioma treatment centers? 21 A. I am not. 22 Q. Has any hospital ever put you in 23 charge of mesothelioma treatment? 24 A. They have not. 25 (Discussion held off the record.)
Page 75 1 A. No. These are things that are 2 outside of my skill set. 3 Q. Okay. Do you know how to do either 4 one of those procedures? 5 A. No, of course not. I'm not a 6 pathologist. 7 Q. How many patients have you seen with 8 mesothelioma in your career? 9 A. I, I don't keep a count. 10 Q. Do you have any kind of estimate? 11 A. No. I think the -- the only way I 12 can come close is that I think in a typical 13 year, you know, since medical school, I've seen 14 approximately one, you know, maybe two at the 15 most, and some years zero. 16 So I think if it was an average of 17 one a year, that might be about right. But I'm 18 not sure that's exactly accurate. 19 Q. And how many years has it been since 20 you graduated medical school? Can you remind 21 me? 22 A. I graduated in 1990. So thirty- -- 23 32. 24 Q. Okay. So you've seen approximately 25 30 or less patients with mesothelioma in your	Page 77 1 (Recess.) 2 BY ATTORNEY ADAMS: 3 Q. Dr. Diette, who do you report to at 4 Johns Hopkins? Is there like a department head 5 or chief or someone who you report to? 6 A. Well, there's a hierarchy. I mean, 7 there's division chief and then a department 8 chair and then the dean; yeah. 9 Q. Who's the division chief of your 10 division? 11 A. Currently, it's John Orens as an 12 interim chief. 13 Q. Who's the department chair? 14 A. Nadia Hansel. 15 Q. And then I forget the other one you 16 said? 17 A. Yeah, there's a new dean. I'll have 18 to see. He just started. But there's a new 19 dean as well. 20 Q. You can't remember his name off the 21 top of your head? 22 A. No. No. 23 Q. Are you aware of anyone who has not 24 been paid by the talc or asbestos industry who 25 says a person can breathe asbestos, develop

Page 78 1 pleural mesothelioma, with proper latency, and 2 it's appropriate to call that spontaneous? 3 ATTORNEY LAWLER: Object to form. 4 THE WITNESS: I don't know where that 5 statement comes from. But I don't -- I 6 would imagine that there's plenty of 7 people that understand the concept of 8 dose. And so -- but I don't know what 9 that statement comes from. 10 BY ATTORNEY ADAMS: 11 Q. Do you think there's plenty of people 12 who understand the concept of individual 13 susceptibility as well? 14 ATTORNEY LAWLER: Object to form. 15 THE WITNESS: So I do think there 16 are -- individual susceptibility to all 17 sorts of things is well understood in 18 medicine and in a continuously emerging, 19 you know, field -- for precision medicine, 20 for example. 21 BY ATTORNEY ADAMS: 22 Q. Are you aware of anyone not paid by 23 the talc or asbestos industry who says a person 24 can have an exposure to asbestos above 25 background, have a proper latency time period	Page 80 1 use that statement other than in litigation, a 2 statement similar to that. But I don't know 3 what an occupational exposure refers to because 4 I think there's a broad range of occupational 5 exposures. 6 You know, like, for example, in these 7 cases there's potential occupational exposures 8 to others other than the plaintiffs themselves. 9 And so whether you call that an occupational 10 exposure, I think people would consider whether 11 or not it's a sufficient or significant exposure 12 as well. 13 Q. Are you aware of anyone not paid by 14 the talc or asbestos industry who says a person 15 can be exposed to asbestos, develop 16 mesothelioma, and that mesothelioma can be 17 appropriately called spontaneous? 18 ATTORNEY LAWLER: Object to form. 19 THE WITNESS: So I don't know of 20 anybody making a statement that's 21 literally exactly that. 22 BY ATTORNEY ADAMS: 23 Q. How many times have you called a 24 woman with pleural -- strike that. 25 How many times have you given the
Page 79 1 pass, develop pleural mesothelioma, and it's 2 appropriate to call that mesothelioma 3 spontaneous? 4 ATTORNEY LAWLER: Object to form. 5 THE WITNESS: So I'd say other than 6 in litigation circumstances, I don't know 7 people that talk about the concept of 8 above background. So I just don't know 9 people one way or the other that referred 10 to above background being like some 11 threshold importance. 12 BY ATTORNEY ADAMS: 13 Q. Are you aware of anyone outside 14 of -- strike that. 15 Are you aware of anyone not paid by 16 the talc or asbestos industry who says a person 17 can have an occupational level of exposure to 18 asbestos -- 19 ATTORNEY LAWLER: Object to form. 20 BY ATTORNEY ADAMS: 21 Q. -- let the proper latency period 22 pass, develop pleural mesothelioma, and it's 23 appropriate to call that mesothelioma 24 spontaneous? 25 A. So I never heard anybody whatsoever	Page 81 1 opinion that a woman with pleural mesothelioma 2 had a spontaneous or naturally occurring 3 mesothelioma? 4 A. Yeah, I don't know the number. 5 Q. Do you have any estimate whatsoever? 6 A. No. You've asked me this before. 7 And I don't keep track of it that way. And even 8 still -- like sometimes if it's a case where 9 we're talking about where the most likely thing 10 is spontaneous, I may also in another case say 11 it's possible, right; because, you know, you can 12 be a heavy smoker and get lung cancer and you 13 can still have something other than smoking, you 14 know, cause it, but I think smoking is the most 15 likely cause. 16 So in some cases, if there's evidence 17 of significant exposures that matter, I'll say 18 that. And if there's not, then spontaneous is 19 what's left. 20 Q. You remember some of the questions 21 that I've asked you before? 22 A. Of course. 23 Q. Do you remember some of the cases 24 that we've worked on together before? 25 A. Hirshberg's the only one I can think

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Page 82 1 of off the top my head. But, you know, I know 2 there's a few others. 3 Q. In every single case we've ever 4 worked on before, you've called my client's 5 mesothelioma spontaneous; correct? 6 ATTORNEY LAWLER: Objection; 7 mischaracterization. 8 THE WITNESS: I don't agree with 9 that. And you remember when we talked 10 about this before, I said we want to look 11 specifically at the report to see what it 12 said; because I may have used the term 13 spontaneous in there, but in some cases it 14 may not have been the most likely 15 scenario. 16 BY ATTORNEY ADAMS: 17 Q. You remember Rita Chapman? 18 A. I do. 19 Q. That was my client right? 20 A. I think that's correct. 21 Q. You called her mesothelioma 22 spontaneous; correct? 23 A. I believe it was. 24 Q. Do you remember Mae Moore? 25 A. I don't remember specifics there.	Page 84 1 A. I do. 2 Q. Go to the very end. Your opinion in 3 the Mae Moore case was [as read]: It is most 4 likely that Mrs. Moore's mesothelioma formed 5 spontaneously or was naturally occurring. 6 Correct? 7 A. It was. But can you do me a favor 8 and just scroll up to the assessment as well. 9 Q. Sure. 10 A. So, yeah. So this is an example, 11 too, where, you know, I allowed for the 12 possibility, because it was what the, the facts 13 were in the case, that she may have had 14 take-home exposures from her grandfather's 15 industrial work. And if there were more 16 information that came in that showed that that 17 was a significant exposure, then I would have 18 up -- my opinion would have been it was an 19 asbestos-induced exposure cancer. 20 But because there wasn't enough 21 evidence about that, the only thing left was 22 spontaneous. And that was my opinion. 23 Q. Ah, I see what at you're saying. 24 In your conclusion, though, you say 25 [as read]: It is more likely that Mrs. Moore's
Page 83 1 Q. Okay. Do you remember giving the 2 opinion that Mae Moore's mesothelioma, pleural 3 mesothelioma was spontaneous? 4 ATTORNEY LAWLER: Objection; 5 foundation. 6 THE WITNESS: Yeah, I don't remember 7 the details of the case. But I would, you 8 know, let the report, if you have it, 9 speak for itself. 10 (Exhibit 25 was marked for 11 identification.) 12 BY ATTORNEY ADAMS: 13 Q. I do. I've marked as Exhibit 25, and 14 I'll show it to you right now. It's dated 15 November 16th, 2021. 16 Are you able to see that document? 17 It says Foley & Mansfield on the front. 18 A. I do. 19 Q. See it's got my name on it, Benjamin 20 Adams? 21 A. I do. 22 Q. Mae Moore versus Johnson & Johnson? 23 A. Correct. I see that. 24 Q. Here's your report in that case dated 25 November 15th, 2021. Do see that?	Page 85 1 mesothelioma formed spontaneously or was 2 naturally occurring. 3 Correct? 4 A. Yeah, that was the statement. And if 5 I were to, you know, expand what I mean by that, 6 absent more information about her grandfather's 7 exposure, assuming there's nothing more 8 forthcoming. 9 Q. Okay. You don't mention anything 10 about her grandfather's exposures in the 11 conclusion section; correct? 12 A. No. But the assessment and the 13 conclusion together is where my opinions are. 14 So I don't -- it doesn't need to be in the 15 conclusion for it to be part of my opinion. I 16 just try to make it, you know, simpler to read 17 the conclusion section. There's some redundancy 18 and there's some other things. But to get my 19 opinions, you actually have to look at the 20 assessment and the conclusions. 21 Q. Do you have any estimate at all about 22 how many times you have said something to the 23 effect of it is most likely that a woman's 24 mesothelioma formed spontaneously or was 25 naturally occurring?

Page 86 1 ATTORNEY LAWLER: Object to form. 2 THE WITNESS: No, I don't have an 3 estimate. I would say it would be in 4 every case where there's no identified 5 significant asbestos exposure and no other 6 exposure or some other sort that was a 7 likely cause -- like, for example, 8 radiation. 9 BY ATTORNEY ADAMS: 10 Q. Okay. And so in Miss Moore's case, 11 you had concluded that there was no evidence of 12 a likely substantial asbestos exposure, and so 13 you concluded that it was likely spontaneous or 14 naturally occurring? 15 A. Exactly right. 16 Q. You made the same conclusion in Wendi 17 Hirshberg's case; correct? 18 ATTORNEY LAWLER: Object to form. 19 THE WITNESS: Yeah. Although if 20 we're talking about these, these details, 21 there may be the same statement. I mean, 22 I'm not disagreeing with you. 23 But I think there were -- you know, I 24 don't remember all the details of each 25 case. But I think there were some	Page 87 1 potential alternative exposures that 2 didn't have enough information for me to 3 conclude that she had an asbestos-induced 4 cancer. 5 But I think it was possible in her, 6 you know, based on what the -- based on 7 what the information was. 8 BY ATTORNEY ADAMS: 9 Q. Are you aware that when Miss Moore 10 died, a tissue digestion was performed? 11 ATTORNEY LAWLER: Objection; assumes 12 facts. 13 THE WITNESS: I'm not aware of that. 14 BY ATTORNEY ADAMS: 15 Q. By both plaintiffs and defendants; 16 were you aware of that? 17 ATTORNEY LAWLER: Same objection. 18 THE WITNESS: As I'm sitting here 19 now, I'm not aware of it. I don't 20 remember what I knew at the time I wrote 21 this report. 22 BY ATTORNEY ADAMS: 23 Q. She was still alive. So at the time 24 you wrote this report, she was still alive; 25 there was no tissue digestion.
Page 88 1 A. Okay. 2 Q. She then passed and a tissue 3 digestion was done by both the plaintiffs -- 4 their expert -- and the defense expert. Were 5 you aware of that? 6 ATTORNEY LAWLER: Object to form. 7 THE WITNESS: Yeah, I'm not aware of 8 that. 9 BY ATTORNEY ADAMS: 10 Q. Okay. When you give an opinion in 11 the mesothelioma case that a woman's 12 mesothelioma is spontaneous, are you held 13 financially responsible in any way for that 14 opinion? 15 ATTORNEY LAWLER: Object to form. 16 THE WITNESS: I don't know what that 17 means. 18 BY ATTORNEY ADAMS: 19 Q. Are you -- if you get it wrong, do 20 you have to give the money back that you've been 21 paid? 22 ATTORNEY LAWLER: Object to form. 23 THE WITNESS: I don't know what the 24 mechanism would be for that. 25 BY ATTORNEY ADAMS:	Page 89 1 Q. If you get it wrong when you call a 2 woman's mesothelioma spontaneous, have you ever 3 been sued for malpractice for anything like 4 that? 5 ATTORNEY LAWLER: Objection; form, 6 badgering. 7 THE WITNESS: So, yeah, I don't think 8 that is malpractice. I think my opinion 9 is solid. And I only give the opinion 10 that I believe in. So to me, there is no 11 malpractice in giving an appropriate 12 opinion based on the facts of the case. 13 But what you're asking specifically, 14 no, that's never happened. 15 BY ATTORNEY ADAMS: 16 Q. Have you ever had any consequence 17 come to you financially for giving an opinion 18 that a woman's mesothelioma was spontaneous when 19 that opinion turned out to be wrong? 20 ATTORNEY LAWLER: Objection. 21 THE WITNESS: I'm not aware of a 22 circumstance where it's turned out to be 23 wrong. 24 BY ATTORNEY ADAMS: 25 Q. Do you even --

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Page 90 1 (Crosstalk.) 2 A. Well, I'm not done. Sorry. 3 But based on what I've had in front 4 of me, available, I'm not aware of a single time 5 that I've been wrong. 6 Q. Do you follow the cases where you 7 give -- 8 ATTORNEY LAWLER: Wait. 9 Does that complete your response, 10 Dr. Diette? 11 BY ATTORNEY ADAMS: 12 Q. Sorry. 13 A. It's enough of an answer. I'll wait 14 for the next question. 15 Q. Do you follow the women you go around 16 the country giving the opinion that their 17 mesotheliomas are spontaneous? Do you follow 18 them after the case is over? 19 ATTORNEY LAWLER: Objection; 20 argumentative, beyond the scope. Well 21 beyond the scope. 22 THE WITNESS: I don't. I don't know 23 how to either. 24 BY ATTORNEY ADAMS: 25 Q. Do you follow any of the women whose	Page 92 1 put in your question, the answer's going 2 to be no. 3 BY ATTORNEY ADAMS: 4 Q. Have you followed up with Mae Moore 5 or her family after calling her mesothelioma 6 spontaneous? 7 ATTORNEY LAWLER: Object to form. 8 THE WITNESS: So again, I don't 9 follow-up after a case. So my answer for 10 Miss Moore in particular is no. And I 11 don't know how to do that either. 12 ATTORNEY LAWLER: I'm going to lodge 13 a continuing objection to this line of 14 questioning. It implies an obligation 15 that has been established -- 16 (Crosstalk.) 17 ATTORNEY ADAMS: I'm going to mark as 18 Exhibit 26 a report from Dr. Gordon in the 19 Mae Moore matter on his tissue digestion. 20 And I will show that to the witness now. 21 (Exhibit 26 was marked for 22 identification.) 23 BY ATTORNEY ADAMS: 24 Q. Do you see what I've marked as 25 Exhibit 26, Doctor, at least part of the cover
Page 91 1 mesotheliomas you've called spontaneous after 2 the clients that hired you resolve the case? 3 ATTORNEY LAWLER: Objection. 4 THE WITNESS: I don't do that. But I 5 don't do any follow-up. You know, once, 6 once the case is over, then that's the end 7 of the case for me. 8 BY ATTORNEY ADAMS: 9 Q. Have you followed up with Wendi 10 Hirshberg at all about her disease? 11 A. I've never spoken to Miss Hirshberg. 12 Q. Do you know whether or not she's 13 alive or dead? 14 A. I do not. 15 Q. Have you followed up with Mae Moore 16 about her mesothelioma that you called 17 spontaneous? 18 ATTORNEY LAWLER: Objection. 19 THE WITNESS: Well, you're asking a 20 question that's a subset of a broader 21 question, which you said have I ever 22 followed up. So you can keep asking me 23 about specific people. But I already said 24 I don't do follow-up, you know, after the 25 case is over. So no matter whose name you	Page 93 1 page? 2 A. I do. 3 Q. August 9th, 2022. And it says Mae 4 Moore on it, correct? 5 A. It does. 6 Q. And then down at the bottom it's 7 signed by Ronald E. Gordon, PhD, professor of 8 pathology. Do see that? 9 A. I do. 10 Q. It's also got the Mount Sinai School 11 of Medicine logo on the top left-hand corner. 12 Do you see that? 13 A. I do. 14 Q. And I've underlined a couple portions 15 here where Dr. Gordon reports finding tremolite 16 and anthophyllite asbestos in Miss Moore's lung 17 tissue. Do you see that? 18 ATTORNEY LAWLER: Object to form. 19 THE WITNESS: I do. 20 BY ATTORNEY ADAMS: 21 Q. Did you say "I do"? 22 A. I did say that. 23 Q. And then Dr. Gordon reports finding 24 talc in Ms. Moore's lymph node tissue. Do you 25 see that?

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Page 94 1 A. I do. 2 Q. And he reports finding no other 3 asbestos; correct? 4 A. I haven't read the whole thing. I 5 don't know what else he said he did or didn't 6 do. 7 Q. Do you see anything on the page I'm 8 displaying right now indicating Dr. Gordon found 9 any other types of asbestos other than tremolite 10 and anthophyllite? 11 ATTORNEY LAWLER: Objection. 12 THE WITNESS: I only see tremolite 13 and anthophyllite on this page. 14 BY ATTORNEY ADAMS: 15 Q. Now, Dr. Gordon is an expert you're 16 familiar with? 17 A. I've seen him involved in some legal 18 cases. 19 Q. Which side typically hires him; do 20 you know? 21 A. I can't say. I think he's been a 22 plaintiff's expert in cases that I've seen. But 23 I have no idea who typically retains him. 24 Q. But he reports finding talc, 25 anthophyllite asbestos, and tremolite asbestos	Page 96 1 A. I do. 2 Q. And then he reports finding in the 3 lymph samples for Mae Moore a Libby amphibole 4 fiber, a tremolite fiber -- that's tremolite 5 asbestos fiber -- an anthophyllite asbestos 6 fiber, and an actinolite asbestos fiber. Do you 7 see that? 8 A. I do. 9 Q. Is finding tremolite asbestos, 10 anthophyllite asbestos, actinolite asbestos, and 11 talc in a person's body consistent with that 12 person having a spontaneous mesothelioma? 13 ATTORNEY LAWLER: Object to form. 14 THE WITNESS: Well, it could be. I 15 mean, Dr. Dodson himself has published 16 that you can find -- in Texas you can find 17 those same fibers in those people with no, 18 you know, occupational asbestos exposure. 19 And those numbers by themselves don't 20 tell me whether that's a meaningful 21 difference compared to background for this 22 particular laboratory or anyone's 23 particular laboratory. 24 So no, that doesn't, that doesn't 25 tell me enough information.
Page 95 1 in Mae Moore's tissue; correct? 2 ATTORNEY LAWLER: Object to form. 3 THE WITNESS: It appears so. 4 ATTORNEY ADAMS: I'm going to mark as 5 Exhibit 27 a report from Dr. Dodson in the 6 same case, the Mae Moore case. 7 (Exhibit 27 was marked for 8 identification.) 9 BY ATTORNEY ADAMS: 10 Q. Are you able to see the cover page of 11 that Exhibit 27, Doctor? 12 A. I am. 13 Q. Okay. See how it says May 31, 2022; 14 case name, Mae Moore? 15 A. I do. 16 Q. And then it says authorization from 17 Mr. Lindsay Weiss at the MGM Law Firm. 18 Do you know her? 19 A. I don't know her. And I don't know 20 that -- unless it's -- I don't know what "MGM 21 Law Firm" refers to. 22 Q. Okay. Then on the second page 23 Dr. Dodson reports finding in the left lung 24 sample tremolite, one tremolite asbestos fiber. 25 Do you see that?	Page 97 1 BY ATTORNEY ADAMS: 2 Q. Who else says that besides you and 3 Dr. Dodson? 4 ATTORNEY LAWLER: Object to form. 5 THE WITNESS: Says what? 6 BY ATTORNEY ADAMS: 7 Q. A person can be diagnosed with 8 pleural mesothelioma; have a tissue digestion 9 performed; find talc, anthophyllite asbestos, 10 tremolite asbestos, and actinolite asbestos and 11 confirm -- and conclude that that pleural 12 mesothelioma was spontaneous? 13 Who says that other than you and, 14 allegedly, Dr. Dodson? 15 ATTORNEY LAWLER: Object to form. 16 THE WITNESS: So I'm not alleging 17 that Dr. Dodson said that, by the way. 18 I'm talking about a paper that he said. 19 And I don't know who else has similar 20 opinions to mine in general. 21 But what I am saying is that when you 22 find mineral fibers in somebody's lung, 23 they have to be in a meaningful amount. 24 Our lungs are open to the outside world, 25 and we accumulate all sorts of dust.

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Page 98 1 So it's not a treasure hunt where you 2 just say, Oh, I found a single fiber of 3 something and that that caused that 4 person's illness. 5 BY ATTORNEY ADAMS: 6 Q. Can you identify any peer-reviewed 7 published study that indicates it's appropriate 8 to call a person's pleural mesothelioma 9 spontaneous when a tissue digestion is performed 10 and talc and three forms of asbestos are found 11 in their tissue? 12 ATTORNEY LAWLER: Objection to the 13 characterization of "appropriate." 14 THE WITNESS: Yeah, it's an absurdly 15 specific question. And what I'm going to 16 say is there is no paper that says that. 17 You actually have to use all the science 18 available to you to make a conclusion like 19 that. 20 So I think, for example, in 21 Dr. Dodson's paper from Texas, he shows 22 that those fibers can be found in people 23 who have no known asbestos exposure from 24 work, for example. And so just finding 25 them all by itself is not an implication	Page 100 1 for there to be a sufficient dose of asbestos -- 2 if we're talking about asbestos -- or some other 3 exposure that's meaningful if it's not asbestos; 4 so, for example, like external beam radiation, 5 you know, as an example. 6 And if there is a sufficient exposure 7 to cause the disease or increase the risk of the 8 disease, than that to me would be an 9 asbestos-induced tumor or radiation-induced 10 tumor or whatever. 11 If there's no meaningful exposure -- 12 you know, there's only three ways you can get 13 mutations, right. You can be born with them or 14 they can spontaneously develop or they can be 15 induced by something exogenous. 16 So if you can't find something 17 exogenous in a sufficient dose to cause the 18 tumor, there's not much left. 19 Q. And so in determining whether or not 20 an individual's mesothelioma is spontaneous, the 21 method that you use is, number one, look at the 22 facts of the case; correct? 23 A. Correct. 24 Q. Look at the -- look at what's known 25 from the medical and scientific literature;
Page 99 1 that they've had a meaningful asbestos 2 exposure. 3 There's by -- you know, the article 4 that summarized the so-called Helsinki 5 criteria, that talks about there being an 6 issue about above laboratory background 7 levels of asbestos findings for them to be 8 meaningful. 9 So I think you have to integrate many 10 things. You're not looking for a simple 11 statement like you just made to pretend 12 that the concept isn't, isn't valid, 13 right. The concept is valid if you can 14 find asbestos fibers in people's lungs in 15 general and not in a meaningful amount. 16 That doesn't mean that's got any causal 17 connection to whatever their cancer is. 18 BY ATTORNEY ADAMS: 19 Q. What is the method or procedure that 20 you use to determine whether or not a person's 21 pleural mesothelioma is spontaneous? 22 A. So I look at all the facts of the 23 case and integrate with what that's -- what's 24 known from the medical and scientific 25 literature. And generally speaking, I'm looking	Page 101 1 correct? 2 A. That's correct. 3 Q. Determine whether or not there is a 4 sufficient dose of asbestos or some other 5 exposure that's meaningful; correct? 6 A. That is correct. 7 Q. And if there is no meaningful 8 exposure to asbestos or another 9 mesothelioma-inducing substance or procedure, 10 then you conclude the mesothelioma was 11 spontaneous; correct? 12 ATTORNEY LAWLER: Object to form. 13 THE WITNESS: Yes. 14 BY ATTORNEY ADAMS: 15 Q. How do you determine whether the 16 mesothelioma was idiopathic? 17 A. So I don't know what you mean by 18 "idiopathic," because people use that term 19 different ways. 20 Q. What's the potential error rate in 21 your process for determining whether or not a 22 person's mesothelioma is spontaneous; do you 23 know? 24 A. I don't know of a measurable error 25 rate. I think that would include having to know

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Page 102 1 some truths about things that sometimes aren't 2 available in the case, right. So, for example 3 if in the cases we have in front of us, if their 4 claimed exposures to other sources of asbestos 5 turn out to be meaningful, then it would be -- 6 if those were meaningful or significant, they 7 might -- well, I don't think -- it would be an 8 error, per se. It would be a correct, a correct 9 opinion based on the available materials. 10 But if it turns out later that, you 11 know, somebody finds out, for example, that the 12 plumber, you know, was actually working with, 13 you know, an awful lot of, like, old 14 asbestos-wrapped piping and brought a lot home, 15 then that would be something where I would 16 adjust my opinion. 17 But as far as it goes with what's 18 available, I'm not aware there is any error. 19 Q. Is part of your method and procedure 20 in determining whether a mesothelioma is 21 spontaneous to ignore positive test results 22 finding asbestos in powder products that the 23 individual used? 24 A. Absolutely not. 25 ATTORNEY IULO: Objection.	Page 104 1 a worst-case scenario would entail, then 2 that's very helpful for me to understand 3 what dose we're talking about. 4 And so it doesn't ignore it. It 5 doesn't assume that there's no, there's no 6 asbestos. I take into account all the 7 information that's available in the case. 8 So that's not the same as ignoring it. 9 And when you're talking about -- you 10 know, putting in front of me a document 11 that I haven't had a chance to scrutinize 12 or look into, you know, about findings and 13 talc fibers, I still have to understand 14 what that means. It's not a treasure-hunt 15 approach, right. I'm not trying to 16 sensationalize the finding in order to try 17 to convince somebody that one fiber of 18 tremolite means something, right. 19 So it's not ignoring it. It's taking 20 it into account, based on what the context 21 is providing. 22 BY ATTORNEY ADAMS: 23 Q. Has your method to determine whether 24 or not a person's mesothelioma is spontaneous 25 been subjected to peer review?
Page 103 1 ATTORNEY LAWLER: Object to form. 2 THE WITNESS: Absolutely not. 3 BY ATTORNEY ADAMS: 4 Q. Would ignoring findings of asbestos 5 in powder products that the victim used for 6 years increase or decrease the error rate in the 7 method by which you determine whether a person's 8 mesothelioma spontaneous? 9 ATTORNEY IULO: Objection. 10 ATTORNEY LAWLER: Objection. 11 THE WITNESS: So it wouldn't, it 12 wouldn't change it based on what I know 13 about the cases that are real cases that 14 we're talking about, right. 15 First of all, I don't ignore it, 16 right. So I acknowledge when there are 17 opinions that say that there was asbestos 18 found in talc. When those are available 19 in the case, I'll consider those. 20 Sometimes there are opinions that say 21 that there isn't asbestos in the talc, and 22 there might be experts that have different 23 opinions. And I can't resolve that. 24 But when I look at, for example, like 25 an industrial hygienist's estimate of what	Page 105 1 A. It's not a method that I've created 2 or would be subjected to peer review. 3 Literally, the information that I use 4 is what comes from the peer-reviewed literature, 5 right. As I said, there's only three ways to 6 get a mutation. And those three ways are 7 something exogenous causing one or to have a 8 genetic defect that you're born with or to form 9 spontaneously. 10 So it's not a method that I've 11 created. It's just an application of the 12 medical and scientific information. 13 BY ATTORNEY ADAMS: 14 Q. The peer-reviewed literature you're 15 referring to is what you cited to me: Spirtas 16 1994, the Henley paper, Moolgavkar's paper, 17 Price and Ware's paper, and Carbone 2019 or 18 2020; correct? 19 A. It includes those. 20 Q. What else does it include? 21 A. Well, it includes everything that 22 I've read, much of which that I've cited in my 23 report. So it doesn't just come from a 24 particular location, right. 25 So I might not have thought of

Page 106 1 Dodson, for example. But since you showed me 2 something with Dr. Dodson's name on it, it 3 reminds me that there's a paper that he has that 4 shows that it's possible to have asbestos fibers 5 in people that don't have occupational exposure 6 to asbestos -- and all six types, by the way. 7 So that's part of the information. 8 If we're going to talk about, you 9 know, what constitutes a rate of spontaneous 10 mutations, you know, that Tomasetti and 11 Vogelstein stuff is very instructive on that. 12 And that's listed in my report. 13 So there isn't just one source of 14 information. It's an accumulated community, you 15 know, knowledge from practicing medicine and 16 understanding, you know, what scientists and 17 doctors talk about how cancer forms. And that's 18 all the information that I use. 19 Q. Is it your opinion that Tomasetti and 20 Vogelstein say that most pleural mesotheliomas 21 in women are spontaneous? 22 ATTORNEY LAWLER: Objection. 23 THE WITNESS: So they don't. They 24 actually don't say that anywhere 25 literally. What they do is they have a	Page 107 1 proportion of driver mutations that's 2 estimated to be from exposure versus 3 spontaneous. And we'd have to look at my 4 report to get the exact number. But I 5 think the proportion of driver mutations 6 for women is about 48 percent. 7 And that's international, right. 8 That's based on international data and 9 particularly heavy on the UK. 10 So it's about -- you know, it's close 11 to 50/50, but I think it's about 48 12 percent. 13 ATTORNEY ADAMS: I'm going to move to 14 strike everything after "they don't." 15 BY ATTORNEY ADAMS: 16 Q. Is it your opinion that Dr. Dodson 17 says that most mesotheliomas in women are 18 spontaneous? 19 ATTORNEY LAWLER: Objection. 20 THE WITNESS: So I want to correct my 21 last answer, because I might have a 22 familiar way of speaking that's not as 23 crisp as you might like. 24 But I think when I said "they don't," 25 I was then thinking about the table and
Page 108 1 what's in my report. 2 But I think my specific answer 3 includes that their estimate is about 4 48 percent of the driver mutations are 5 spontaneous mutations for women with 6 regard to mesothelioma. 7 BY ATTORNEY ADAMS: 8 Q. Did Tomasetti and Vogelstein ever say 9 anywhere at any time most mesotheliomas in women 10 are spontaneous? 11 ATTORNEY LAWLER: Object to form. 12 THE WITNESS: There's no statement 13 like that. And they don't mention it for 14 many of the tumor types that they've 15 included in their paper. 16 BY ATTORNEY ADAMS: 17 Q. Does Dr. Dodson ever say anywhere 18 that you've ever read at any time that most 19 mesotheliomas in women are spontaneous? 20 ATTORNEY LAWLER: Objection. 21 THE WITNESS: I can't recall if he 22 has or not. 23 BY ATTORNEY ADAMS: 24 Q. Can you recall any other 25 peer-reviewed published study or author who says	Page 109 1 that who you have not already referenced? 2 A. I think we've talked about several. 3 I can't think of others off to top of my head. 4 But I will say -- actually, I take 5 that back. You know, there is -- a couple years 6 ago I did a citation search for who has cited 7 the Spirtas article. And so I think -- I can't 8 tell you today sitting here. But there's a way 9 to link back the many, many articles that have 10 cited the Spirtas and supported a statement 11 along those lines. 12 So I can't recall what they all are, 13 but the Spirtas article's been cited by many 14 other authors. 15 Q. Do you believe your method of 16 determining whether or not a pleural 17 mesothelioma is spontaneous has been accepted in 18 the relevant scientific community? 19 ATTORNEY LAWLER: Object to form. 20 THE WITNESS: I think my method is 21 not unique to mesothelioma. You asked me 22 about mesothelioma. But I think it's in 23 general the same approach that my peers 24 use for thinking about cancer causation, 25 right. It's not unique to mesothelioma.

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Page 110 1 People consider the exposures that 2 they know are relevant. And in many cases 3 there aren't known relevant exposures; and 4 then you're left with nature, you know, 5 being the explanation for it. 6 And in some tumor types, where 7 there's very little known about 8 environmental exposure, that there -- you 9 know, it's just basically assumed that 10 it's most likely to be a naturally 11 occurring one. And I'll give you an 12 example of like, you know, spinal cord 13 cancer, which is a rare cancer that 14 doesn't have much known about exposures 15 that could increase the risk of it. 16 BY ATTORNEY ADAMS: 17 Q. Do you believe your method of 18 determining that there has been no meaningful 19 exposure for the inducement of mesothelioma and 20 therefore it must be a spontaneous mesothelioma 21 has been accepted in the relevant scientific 22 community? 23 A. So I think in general the principles 24 that I'm applying -- it's not my method, right. 25 I'm applying the methodology that's available to	Page 112 1 spontaneous versus idiopathic? 2 ATTORNEY LAWLER: Object to form. 3 THE WITNESS: I don't know what you 4 mean by "idiopathic." 5 BY ATTORNEY ADAMS: 6 Q. Unknown cause. 7 A. Yeah, I don't know. See, 8 idiopathic's a word -- so if that's -- that's 9 your definition. I think idiopathic has meant a 10 lot of things, and it changes over time. I know 11 some people -- I hear colleagues talking about 12 idiopathic versus spontaneous interchangeably. 13 And to me, idiopathic means that 14 there is a, there is a cause, right, that just 15 has been discovered yet; there's some exogenous 16 cause. 17 And so I don't, I don't know how that 18 kind of fits into the conversation we're having. 19 I don't recognize that there's something called 20 idiopathic that means something different here 21 than spontaneous. 22 Q. Here's the National Cancer 23 Institute's definition. Have you ever looked 24 that up? 25 A. I don't know if I have or not.
Page 111 1 all of us, which is looking, for example, for 2 environmental exposures that are known to induce 3 a cancer. And it's baked into what my peers and 4 I do on a regular basis. 5 If somebody has lung cancer and 6 they've smoked, you know, 40 pack-years of 7 tobacco, then there's going to be an assumption 8 made that we can't prove, right. There's no 9 biomarker in the lung tissue to say that is from 10 tobacco. But there's going to be an assumption 11 that it's a tobacco-induced cancer. 12 We're faced all the time, and 13 increasingly so, with people who come into the 14 clinic that have lung cancer diagnosed, for 15 example, and they never smoked and they don't 16 have any industrial exposure and they don't have 17 anything else to explain it. 18 So in those cases we're left with it 19 being naturally occurring. And whether you use 20 the term "spontaneous" or "naturally occurring," 21 you're talking about something that didn't 22 require, you know, something from outside the 23 body in order to come and induce that cancer. 24 Q. What's the standard in your 25 methodology for determining a mesothelioma is	Page 113 1 Q. I just did. [As read]: Idiopathic 2 describes a disease of unknown cause. 3 Do you agree or disagree with the 4 National Cancer Institute's definition of 5 idiopathic? 6 ATTORNEY LAWLER: Objection. 7 THE WITNESS: I don't know. I don't 8 embrace that. I think it's a -- I think 9 it's one way that people use that term. 10 But it implies that there's a cause that 11 just hasn't been discovered. And it 12 doesn't mean that there will be one that's 13 discovered. But it just -- it's a 14 placeholder sometimes in people's 15 thinking. 16 BY ATTORNEY ADAMS: 17 Q. Do you have a standard in the 18 methodology that you use to determine whether a 19 mesothelioma is idiopathic or spontaneous, or 20 no? 21 A. So I don't think I can answer your 22 question because you keep asking me about 23 idiopathic and I told you that I don't think 24 it's relevant for the conversation that we're 25 having. Like I don't recognize that there is

Page 114 1 such a thing as idiopathic mesothelioma. I 2 think it may be a term that people use; and I 3 wouldn't criticize them for it, necessarily. 4 But it doesn't mean anything to me. 5 I think that there are established 6 causes of mesothelioma that are exogenous. And 7 I think spontaneous is -- spontaneity is a way 8 for a -- for any tumor to potentially form, 9 including mesothelioma. 10 Q. Since you don't believe the word 11 idiopathic applies to mesothelioma, you don't 12 have a standard to control your methodology for 13 determining between a spontaneous and idiopathic 14 mesothelioma; correct? 15 A. No, that's nonsense. 16 ATTORNEY LAWLER: Objection. 17 THE WITNESS: What I'm saying is 18 idiopathic refers in this context to 19 something or somebody believes there's an 20 exposure that hasn't been found or 21 identified yet. And I don't know what 22 we're talking about there. That's why I 23 said I don't recognize that for this. 24 I think there are known exposures, 25 right, and there's also the opportunities	Page 116 1 asbestos exposures and then talc. 2 I would say in the last year I 3 probably made somewhere between 100- and 200,000 4 from talc-related cases and probably on that 5 order of magnitude for asbestos that's not talc. 6 There's been, you know, years where I 7 make nothing from those. And probably two years 8 ago I probably made a bit more than that. 9 Q. Do you have any estimate of the total 10 amount of money you've made working in asbestos 11 and talc litigation? 12 A. I don't. 13 ATTORNEY LAWLER: Object to form. 14 THE WITNESS: Yeah, I don't. 15 BY ATTORNEY ADAMS: 16 Q. No estimate at all? 17 A. I don't. 18 Q. Is it more or less than \$10 million? 19 A. Well, it can't be \$10 million. But I 20 don't have an estimate. 21 Q. Is it more or less than \$5 million? 22 ATTORNEY LAWLER: Objection; 23 cumulative. 24 THE WITNESS: Yeah, I don't think it 25 can be anywhere near that.
Page 115 1 for cells to get a mutation spontaneously. 2 And that's kind of the universe that 3 exists for cancers at this point. 4 BY ATTORNEY ADAMS: 5 Q. Since it's nonsense, you don't have a 6 methodology that determines whether or not a 7 mesothelioma is spontaneous or idiopathic; 8 correct? 9 ATTORNEY LAWLER: Objection. 10 THE WITNESS: I can't answer the 11 question and I keep telling you why I 12 cannot, and so I'm not going to try 13 anymore. 14 BY ATTORNEY ADAMS: 15 Q. How much money have you made working 16 in asbestos litigation? 17 ATTORNEY LAWLER: Object to form. 18 THE WITNESS: I don't have a 19 cumulative amount. 20 BY ATTORNEY ADAMS: 21 Q. Do you have any estimate whatsoever 22 of the money you've made in asbestos litigation? 23 A. So I can tell you, I've sorted 24 separately with asbestos and talc. So there are 25 some cases that involve, you know, traditional	Page 117 1 BY ATTORNEY ADAMS: 2 Q. Is it more or less than \$2 million? 3 ATTORNEY LAWLER: Objection. 4 THE WITNESS: I doubt it, but I don't 5 have an estimate. 6 BY ATTORNEY ADAMS: 7 Q. Who assists you in your talc and 8 asbestos litigation? 9 A. Well, there's folks that work at a 10 company called Medical Science Affiliates that 11 provide administrative support. 12 Q. How did you get in contact with 13 Medical Science Affiliates? 14 A. Many, many years ago a colleague of 15 mine knew somebody who worked there. And they 16 were looking for somebody who was an 17 epidemiologist to conduct an epidemiologic 18 review. And so I got connected with them that 19 way. 20 Q. Do you know what year that was? 21 A. I don't -- 22 (Crosstalk.) 23 Q. Sorry. 24 A. No, that's all right. 25 I was going to say it's got to be at

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Page 118 1 least 15 years ago. But I don't know how long 2 ago. 3 Q. How much money did you make last year 4 working in asbestos and talc litigation? You 5 may have just told me, but can you just repeat 6 it. 7 A. Yeah, I did. I think my estimate was 8 somewhere between 100- and 200,000 for each of 9 those two categories, but I think maybe a little 10 less in terms of asbestos, per se, as opposed to 11 talc. 12 Q. So roughly between -- strike that. 13 In 2022 you made roughly 200- 14 to \$400,000 working in asbestos and talc 15 litigation? 16 A. I think that's a reasonable estimate. 17 Q. Who are the individuals at Medical 18 Science Affiliates that provide administrative 19 support for you in talc litigation? 20 A. Well, Madalyn Pettenati has been the 21 primary one. And then there's other, other 22 folks that I don't interact with directly but -- 23 you know, people who, you know, prepare 24 materials or photocopy papers and other things. 25 Q. Can you spell Madalyn's last name?	Page 120 1 to you? 2 A. \$600. 3 Q. You also have a four-hour minimum for 4 travel if you travel more than 60 miles from 5 your home or office; correct? 6 A. That's right. 7 Q. And so if you travel 90 miles from 8 your office for a case, you bill a minimum of 9 \$2900; correct? 10 A. Um... 11 Q. It's 4 times 725. 12 A. Oh, okay. That sounds right, then, 13 yeah. Although I personally would charge 2400 14 for that, not the amount you said. 15 Q. 500 goes to Med Science Affiliates 16 and 2400 goes to you? 17 A. That's correct. 18 Q. Your hourly rate goes up by \$200 an 19 hour for deposition testimony; correct? 20 A. That's right. 21 Q. Why is that? 22 A. Well, two things. One, so my 23 personal rate is 700. So it goes up by a 24 hundred for me. 25 And it's, it's generally more work.
Page 119 1 A. Maybe. It's -- I think it's 2 P-E-T-T-A-N-I-T-I [sic]. 3 Q. Is there anyone outside of Medical 4 Science Affiliates that assists you with your 5 work in asbestos and talc litigation? 6 A. No. 7 Q. Your fee schedule indicates that your 8 billable rate is 725 an hour, correct, your 9 baseline billable rate? 10 A. Yeah. Although, for me it's \$650 an 11 hour -- or, I'm sorry, \$600 an hour. 12 Q. The portion that you receive is 600 13 an hour? 14 A. Well, I get a hundred percent of what 15 I asked for, right. So I ask for \$600 an hour. 16 And then Medical Science Affiliates has a 17 business model where they add something to that 18 for some of their work. 19 Q. Okay. How much goes to you? 20 A. Well, the 600 that I ask for. 21 Q. Got it. You also have a travel 22 policy where you bill \$725 per hour for travel; 23 correct? 24 A. That's correct. 25 Q. How much of that 725 for travel goes	Page 121 1 You know, it's -- like, qualitatively, I think 2 it's a different type of work than, you know, 3 sitting and reading materials and or, you know, 4 drafting a report and that type of thing. 5 Q. Who typically pays for your 6 deposition testimony, the defendants or the 7 plaintiff? 8 A. I would assume whoever's taking the 9 deposition, you know, would pay for. But I 10 don't know that that's uniformly true. 11 Q. Who's usually taking the deposition, 12 lawyers for the plaintiff or lawyers for the 13 defendants? 14 A. Oh, it depends upon the case. We're 15 talking just about the talc cases? 16 Q. Yes. 17 A. Yeah, so in talc cases, it's always 18 the plaintiffs. 19 Q. And so in talc cases, the plaintiffs 20 always pay your bill for the depositions; 21 correct? 22 A. It's my intent. I don't know if I've 23 kept track well enough to know that they always 24 do. 25 Q. You have a 4-hour minimum for

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Page 122 1 depositions? 2 A. That's correct. 3 Q. Does that mean that you get paid for 4 4 hours of time even if the deposition lasts 5 only an hour? 6 A. It does. 7 Q. So if the depo lasts 1 hour, you 8 request to be paid \$3700? 9 A. I do; unless we had some agreement in 10 advance, you know, that somebody knew it was 11 only going to be an hour, for example. But if 12 there's no agreement, then I have to block out a 13 chunk of time, and I bill for it. 14 Q. You have a cancellation policy -- 15 wait. Sorry. 16 How do you bill your time when you 17 travel? And what I'm asking is: Do you bill 18 from the time you leave your door until you get 19 home? Do you bill an 8-hour minimum every day? 20 Do you bill some other increment? 21 How do you bill when you travel? 22 A. So not, not from door to door. Like, 23 I don't mean from the minute I leave the door. 24 I think if it's a full day of travel, it would 25 be, you know, 8 hours, you know, if it's	Page 124 1 Q. Okay. We're going to have to figure 2 that out, then. 3 A. I think, just to help you, I don't 4 think there's any of my time on there. So I 5 don't think there's -- whether it's 28,000 or 6 not, I don't think that there's any billable 7 time for me on there. 8 Q. What does that mean? 9 A. I think this was all, all time billed 10 to MSA staff. 11 Q. Have you billed any money in the 12 Sarah Plant case? 13 A. I have not. 14 Q. Have you made any money in the Sarah 15 Plant case? 16 A. I can't think how that would work. 17 But no. No, I just haven't submitted a bill 18 yet. 19 Q. Have you spent any time working on 20 the Sarah Plant case? 21 A. Oh, yeah, of course. 22 Q. How much? 23 A. Probably in the -- somewhere in the 24 20-to-30-hour range, 20 to 30. 25 Q. And has that been at 725 an hour --
Page 123 1 approximately that. 2 I don't think it's happened. But, 3 like, if it took 36 hours of, you know, train 4 time or something, I guess I would bill 36 5 hours. 6 But that hasn't happened. So it's 7 basically, like, a day's kind of a day. 8 Q. You have a cancellation policy for 9 travel; correct? 10 A. I do. 11 Q. If a deposition or trial testimony 12 that requires travel is canceled less than a 13 week before the event, you charge \$5800; 14 correct? 15 A. Well, that's what the paper says. 16 I've actually never done that. And things get 17 canceled all the time at the last second. So I 18 have never invoked it, but I just -- I aspire to 19 it. 20 Q. Got it. You produced a number of 21 invoices in the Plant matter. I added them up. 22 It added up to \$28,402.47. Does that sound 23 right? 24 A. Oh, I have no idea. I didn't look 25 at -- I mean, I didn't look at the totals.	Page 125 1 or 600 an hour? 2 A. So I think -- so I literally just 3 changed the fee schedule like a couple weeks 4 ago. So I don't think any of the time would 5 actually be billed at these rates that you see 6 here. I think it was 650 before and 550 that I 7 billed. So I think most of what we're talking 8 about would be, to me personally, would be 550 9 an hour for that time. 10 Q. So you've billed approximately 15-, 11 16,000 -- strike that. 12 Dr. Diette, you have -- strike that. 13 Dr. Diette, the time you've spent 14 working on this case, you expect to be paid 15 approximately 15-, \$16,000 so far before today; 16 fair? 17 A. That sounds right. 18 Q. And I'm referring to the Sarah Plant 19 case; you understand? 20 A. I do. 21 Q. In the Shelby Payne case, how much 22 time have you spent working on that case? 23 A. I'd estimate a similar amount to the 24 Plant case. 25 Q. So for the -- as of February -- I'll

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Page 126 1 go with yesterday -- 2nd, 2023, you expect to be 2 paid for your work in the Payne and Plant cases 3 somewhere around \$30,000? 4 A. For the two together, did you say? 5 Q. Yeah. 6 A. Yeah, that sounds about right. 7 Q. And that doesn't include the 8 deposition today; correct? 9 A. That is correct. 10 Q. For which you expect to be paid 11 another -- 12 A. I can tell you. 2800. 13 Q. 2800. So as of February 3rd, 2023, 14 you expect to be paid approximately \$3,280, 15 roughly, for these two cases, the Sarah Plant 16 and Shelby Payne cases; correct? 17 A. Did you say 3,000 or -- it sounded 18 like 3. There's 30,000. 19 Q. I'll try again. As of today, 20 February 3rd, 2023, you expect to be paid for 21 your work in the Shelby Payne and Sarah Plant 22 cases approximately \$32,800? 23 A. That, that sounds like a good 24 estimate. 25 Q. Okay. You listed a number of other,	Page 128 1 analysis, you know, of the case. 2 Q. Did Sarah Plant have any diseases, 3 conditions, or co-morbidities that you found, 4 within a reasonable degree of medical certainty, 5 would have shortened her life expectancy? 6 A. Well, I think it's possible that her 7 BRCA2 gene mutation has the potential. But I 8 haven't, I haven't analyzed that. But she is at 9 risk for other cancers. And so I think, you 10 know, one would want to take that into account, 11 you know, in sort of thinking about that 12 question. 13 Q. Can you go farther than "possible"? 14 A. Possible shortening or possible risk 15 of cancer? 16 Q. Shortening of life. 17 A. Oh, yeah, no, I can't. I mean, I 18 don't -- I haven't, I haven't been tasked with 19 putting the work in to try to determine whether 20 there would be shortening or how much that would 21 be. 22 ATTORNEY ADAMS: All right. Those 23 are all the questions I have for you 24 today, Dr. Diette. I appreciate your 25 time.
Page 127 1 sort of, medical conditions that Miss Payne had 2 in your report. Do you know what I'm referring 3 to? 4 A. Well, I'll just say maybe, because 5 there is a -- there's many medical conditions 6 that are sort of captured within the, like the 7 notes themselves. But there's also a section -- 8 let me see if I've got the right report -- also 9 called Past Medical History. Is that what 10 you're referring to? 11 Q. I can't remember. But I remember 12 seeing you list, you know, things like skin 13 cancer, I think. Let me see if I can find it. 14 A. I can tell you -- so -- 15 Q. Yeah. Past medical history you've 16 got. Arthritis, anxiety, rib fractures. You 17 know, goes on and on. Do you know what I'm 18 talking about? 19 A. I do. 20 Q. Spider bite. 21 Did Miss Payne have any diseases or 22 co-morbidities that you believe, within a 23 reasonable degree of medical certainty, would 24 have shortened her life expectancy? 25 A. So I haven't done that sort of	Page 129 1 THE WITNESS: Thank you, Mr. Adams. 2 ATTORNEY ADAMS: Does anyone else 3 have any questions? 4 ATTORNEY LAWLER: This is Katherine 5 Lawler for Colgate-Palmolive Company, as a 6 successor-in-interest to the Mennen 7 Company. I do not have any questions for 8 this witness. But I would like to attach 9 as, I believe it's Exhibit 28, 10 Colgate-Palmolive Company's objections to 11 the deposition notices that were 12 previously attached as exhibits. 13 (Exhibit 28 was marked for 14 identification.) 15 ATTORNEY ADAMS: Anyone else have 16 anything? 17 All right. I think can go off the 18 record, then. 19 (Deposition concluded at 1:17 p.m.) 20 21 22 23 24 25

1 CERTIFICATION

2

3

4 I, ADAM D. MILLER, Registered

5 Professional Reporter, certify that the

6 foregoing is a true and accurate transcript

7 of the foregoing deposition, that the

8 witness was first sworn by me at the time,

9 place and on the date herein before set

10 forth.

11 I further certify that I am neither

12 attorney nor counsel for, not related to nor

13 employed by any of the parties to the action

14 in which this deposition was taken; further,

15 that I am not a relative or employee of any

16 attorney or counsel employed in this case,

17 nor am I financially interested in this

18 action.

19

20

21 /s/ Adam D. Miller

Registered Professional Reporter

22 and Notary Public

23

24

25

EXHIBIT 4

3**Mesothelioma: Is There a Background?****J. CORBETT MCDONALD**Royal Brompton National Heart and Lung
Institute
London, England**ALISON D. MCDONALD**McGill University
Montreal, Quebec, Canada**I. Introduction**

Malignant mesothelioma came into prominence, and its existence as a pathological entity was established with publication, in 1958 and the early 1960s, of its frequent occurrence in the crocidolite mining area of South Africa and as a substantial risk for insulation workers and related trades. With hindsight, it is evident that a small number of case reports and small case series with similar work exposure had appeared in the medical literature over the previous 20 or so years. Since then, the full magnitude of the asbestos-related epidemic of mesothelioma has become all too obvious, with incidence continuing to rise in most industrial countries at up to 10% per annum, a trend unlikely to slacken until well into the next century.

In direct consequence of these disastrous events, there is the growing question of whether all cases of mesothelioma have resulted directly or indirectly from the industrial exploitation and use of asbestos. The question has obvious medicolegal importance: if not all cases are so caused, there will always be an element of doubt in attributing a particular case to some specific occupationally related exposure, an idea that plaintiffs' lawyers

would like to dismiss and the defense to promote. The question has also much scientific relevance, in that without full understanding of the agents that can cause mesothelioma, it may be difficult to find safe and satisfactory substitutes for the many important uses of asbestos.

In this chapter we review the main evidence now available on whether there is or has been a background incidence of mesothelioma in humans, unrelated to the industrial use of asbestos. Background cases could have resulted from airborne asbestos or other natural mineral fibers liberated by wind and water erosion from the almost ubiquitous distribution of deposits in the earth's surface, or they could have an entirely different etiology. In assessing the evidence, uncertainty over diagnosis is an everpresent problem, especially in earlier times, when the very existence of primary malignant mesothelioma tumors was doubted, and use of the diagnosis was actively discouraged by such eminent pathologists as Willis (1). Even today, far from all cases are confirmed pathologically and, of those that are studied at autopsy and with the most sophisticated histological, biochemical, and immunological tests, the diagnosis in many is left in doubt. Inevitably these problems are particularly acute when the etiological circumstances are unusual as, for example, in childhood cases or in agricultural regions of distant and developing countries.

II. Historical Evidence

Asbestos was first mined and milled for industrial purposes in the 1870s, but in only small quantities until after World War I. If one considers that the latent period between first exposure and death is usually 30–40 years, and very seldom less than 20 years, it is reasonable to believe that the case reports and case series of the 1930s and 1940s were possibly asbestos-related, whereas it is quite improbable that cases documented before about 1900 were caused in this way. Among the several early papers, mostly by pathologists, on primary pleural malignancies—usually referred to at that time as pleural endotheliomas—those by Robertson in 1924 (2) and Saccone and Coblentz in 1943 (3) were particularly informative. It is clear from both these sources that, aside from the remarkable, but insufficiently validated, report by Lieutaud in 1767 of two pleural tumors among 3000 autopsies and first recognition of the pathological entity by Wagner in 1870, several large autopsy series published at the end of the last century and from 1900 to about 1920 included cases that cannot easily be attributed to the industrial use of asbestos. The frequency of such cases was approximately 1:1000 autopsies, a proportion that unfortunately cannot be related to any population denominator. It is worth noting, nevertheless, that cases ascer-

tained through pathologists across Canada in the early 1960s, before the present upward trend in incidence was evident, constituted a roughly similar proportion of all autopsies. Other analyses made by Saccone and Coblentz included data from two autopsy series, comprising some 150 cases in Germany, published in 1924 and 1931, and unlikely to have been seriously contaminated by occupational asbestos exposure. These cases showed a male preponderance of 1.7:1 and the following age distribution: younger than 21, 4 cases; 21–40, 26; 41–60, 66; older than 60, 33. Without appropriate denominators these figures cannot really be interpreted, but once again, the pattern is similar to that for Canada in 1960–1968.

III. Direct Evidence

The clearest support for the existence of a background unrelated to the industrial use of asbestos is provided by evidence that exposure to other agents or to asbestos fibers in nonoccupational circumstances has also caused the disease. The most compelling indication of this is the extraordinary mortality from mesothelioma in certain villages of Cappadocia, central Turkey, reported by Baris and his colleagues in the 1970s (4). Extensive epidemiological and environmental surveys have strongly supported the hypothesis that the main, but not necessarily the only, causal factor has been exposure from birth to erionite dust, a crystalline fibrous form of the mineral zeolite. In three affected villages, 29 of 125 deaths during a defined period were from pleural mesothelioma, and 4 were from peritoneal mesothelioma (5). The affected villages had higher airborne concentrations of fibers of erionite than an unaffected village. Sheep lungs from the affected villages also had a higher erionite fiber content, although the difference was not statistically significant. Sputum samples from persons living in affected villages contained ferruginous erionite bodies. Age- and sex-specific death rates rose steeply in both sexes, compatible with exposure to a causative agent starting at birth. The youngest case reported in two of the three affected villages was in a man aged 27 years, suggesting that mesothelioma in children, as recorded elsewhere, is unlikely to be due to this type of environmental exposure. There is suggestive, but inconclusive, evidence that erionite deposits in other locations have contributed to mesothelioma incidence. In North America, there was a small, although not statistically significant, excess of cases in proximity to naturally occurring zeolite deposits (6). Also, in a geographic mortality study of pleural mesothelioma in the United States, the authors noted relatively high rates in two Rocky Mountain states and questioned whether these might possibly be explained in this way (7).

Occupational exposure to dust containing fibers in the tremolite series of amphibole minerals has also been associated with a substantial risk of mesothelioma (8). Fibrous tremolite, although very seldom exploited industrially, is nevertheless classifiable as an asbestos fiber, and occupational cases attributable to its commercial production and use cannot be considered as part of any background. The same is true of mesothelioma resulting from occupational exposure in chrysotile mining and milling for which tremolite fiber contamination is suspected of making a disproportionate contribution to the risk. Fibrous tremolite is a common contaminant of various minerals in the earth's crust, some of which are exploited commercially and some not. It is thus conceivable that tremolite fibers liberated by water and wind erosion could contribute to the occurrence of background cases. This possibility is difficult to test, but notably, lung burden analyses, based on 78 Canadian mesothelioma cases and matched controls, showed a significant excess of tremolite fibers (9). Most of this excess may well have resulted from direct or indirect exposure to tremolite contamination of chrysotile in commercial use, but not necessarily all of it. The reality of the latter possibility is demonstrated in northeast Corsica, where general environmental exposure to tremolite and chrysotile fibers has occurred as a result of numerous mineral outcrops in that region (10). A radiographic survey of patients without occupational exposure showed a significantly higher prevalence of bilateral pleural plaques in northeast Corsican residents (3.66%) than in those from the northwest (1.14%), where similar outcrops do not occur. Five cases of pleural mesothelioma were also recorded in patients from the northeast without occupational asbestos exposure, and these were said to have a heavy pulmonary asbestos burden. However, no comparable data were reported for the northwest. Suggestive evidence of a similar nature has also been reported from Cyprus (11) and certain villages in Greece (12), with indications in both that fibrous tremolite could have been responsible.

Over the years, many other chemical, physical, and biological agents have come under suspicion in relation to the sporadic occurrence of mesothelioma in humans and animals, apparently unrelated to asbestos exposure, but the evidence is largely anecdotal and uncontrolled (13). Less easy to dismiss are reports of cases of mesothelioma in sugar cane workers in India (14) and of excess mortality from this cause in southern Louisiana (15). After the harvest the cane is burned off, leading to the formation of long thin respirable silica fibers (16), a process that presumably might also arise in forest fires and other agricultural circumstances. Currently, there are too few epidemiological, experimental, or lung-burden studies to evaluate any of these hypotheses.

IV. Circumstantial Evidence

A. Mesothelioma in Children

It is very unlikely that childhood cases could be due to asbestos exposure because the shortest latent period for which there is reasonably firm evidence is 14 years (17), nor is there any indication that the length of the latent period is affected by age. In a critical review, published in 1964, Kaufman and Stout (18) concluded that, after exclusion of dubious cases, there remained ten, ranging in age from a few months to 14 years—seven in boys and three in girls—for which the diagnosis was thought reliable. All ten were pleural and were more frequently fibrous than tubular or tubulopapillary, as are those in adults. The earliest two cases in the series had been published first in 1886 and 1904, respectively. In a recent review of 80 cases of mesothelioma in children reported 1869–1986 (19), including some of the ten just mentioned, 67.5% were pleural, 25% peritoneal, and 7.5% pericardial. Their ages ranged from 1 to 19 years (mean 9.7 years), with a male/female ratio of 1.4. In only 2 of the 80 cases was there a history of possible exposure to asbestos, 1 in a 3-year-old girl, whose father worked in an insulation plant, and the other in a 17-year-old girl possibly exposed at school. The incidence of mesothelioma in children younger than 20 years of age can be roughly estimated from three studies. In our own Canadian survey, 1960–1968, four fatal cases were ascertained by systematic inquiry from all pathologists—a rate of about 0.7:10 million per annum (20). A very similar figure can be derived from the 13 cases identified by Grundy and Miller (21) among death certificates in the United States of America, 1965–1968. Finally, Cooper et al. (22), using data from the Surveillance, Epidemiology, and End Result (SEER) program in the United States of America, 1973–84, estimated the case incidence at 0.5:10 million per annum. As mesothelioma in children may well be underdiagnosed, a conservative estimate for the annual case incidence in North America is likely to be at least 1:10 million per annum, but even so, appreciably lower than any comparable estimate for adults.

B. Mortality Trends in Men and Women

The short clinical course of mesothelioma from first symptom to fatal outcome, almost always within 2 years, implies that mortality rates closely parallel incidence rates. Mesothelioma has only recently been given a unique code in the International Classification of Diseases, so that, in the past, satisfactory ascertainment was difficult from death certificates. In Canada, annual incidence rates based on cases ascertained through pathologists, when extrapolated backward, suggest that male and female rates were

similar at or before 1950, at a level of about 1-2 per million population (23). This pattern is similar to trends found in the SEER cancer surveillance program of the United States of America (24) and for mortality observed in Britain, Finland, Norway, and Denmark (8). The increasing male excess appears due to the much more frequent history of occupational asbestos exposure in men than in women. In the SEER program, regions with higher age-adjusted incidence rates for mesothelioma in white males, presumably attributable to work-related asbestos exposure, had a higher ratio of male to female cases than regions with lower rates. This is illustrated in Figure 1, in which linear extrapolation would suggest that, at the point where the sex ratio is equal, the incidence would be about 5 per million, although with wide confidence limits. In Los Angeles County equal numbers of cases in

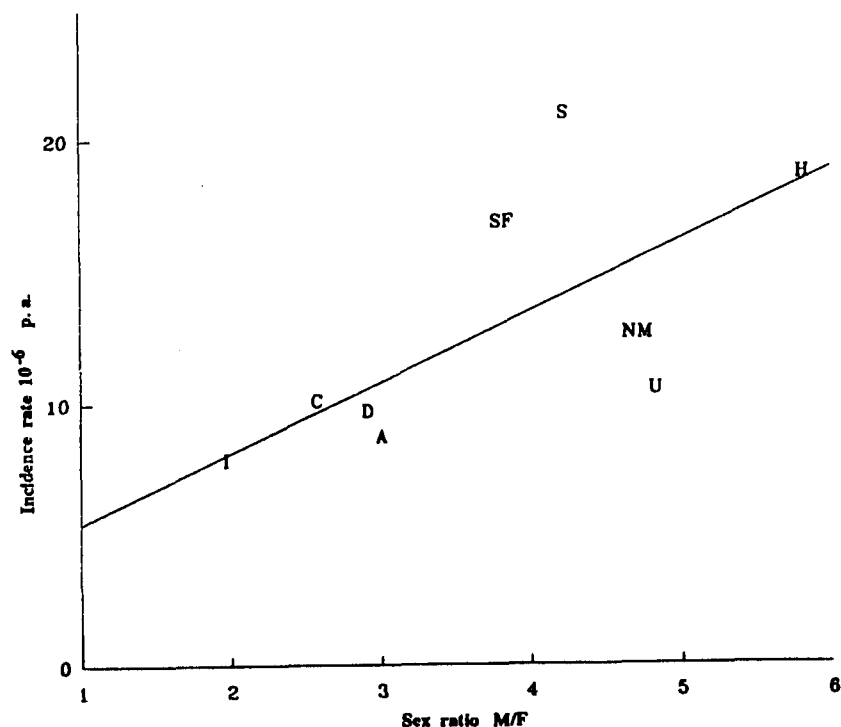


Figure 1 Mesothelioma age-adjusted incidence rates in white males and sex ratios by geographic area, United States of America, 1973-1984 (24). A, Atlanta; C, Connecticut; D, Detroit; H, Hawaii; I, Iowa; N, New Mexico; S, Seattle; SF, San Francisco-Oakland. Trend line fitted by least squares.

men and women were without history of exposure to asbestos, suggesting a background incidence of about 2 per million (25). In France, careful inquiry failed to identify any opportunity for asbestos exposure in younger subjects with mesothelioma; these included equal numbers of males and females (26). In all these various studies, efforts to detect causes other than asbestos have been largely unsuccessful, although in a few cases there has been mention of chronic inflammation and exposure to ionizing radiation or beryllium (27).

V. Analyses of Lung Burden

Evidence of an etiological agent other than asbestos could conceivably have been detected in lung burden analyses. This has not been demonstrated in the few studies yet reported, although these have been confined to the identification and examination of mineral fibers. In two investigations of mesothelioma cases and controls in North America, the first in 1972 (28) and the second in 1979-1984 (9), a substantial excess of amphibole fibers was seen. In the latter study discrimination between cases and controls was almost wholly due to long fibers ($\geq 8 \mu\text{m}$), which it was estimated could explain about two-thirds of the cases. Altogether, 25 varieties of mineral fiber were recognized by electron microscopy but, apart from the amphibole fiber types, no important difference was observed between cases and controls. In the first of the studies mentioned, based on 99 case-control pairs, in 2, neither amphibole nor chrysotile fiber was detected. In the second study, based on 78 pairs, neither chrysotile nor any amphibole fibers were detected in 1 case; on the other hand, no long asbestos fibers ($> 8 \mu\text{m}$) were seen in 14 cases. A similar study in the United Kingdom, although not entirely comparable, gave much the same result (29). These three sets of data are thus compatible with a background incidence unrelated to asbestos, but the evidence is weakened by the few cases studied and limits of detectability by the electron microscopic techniques used. There is also the question of the extent to which postmortem analyses adequately reflect exposures that occurred many years earlier.

VI. Conclusion

All five types of evidence considered in this review point to the existence of a background incidence of primary mesothelial malignancies unrelated directly or indirectly to exposure from the production or industrial use of asbestos, although with varying levels of certainty. The disastrous experience of certain villages in Cappadocia puts the proposition beyond doubt,

but there is little to indicate whether or not the fibrous zeolites have caused the disease elsewhere. Indeed, it would appear that the liberation of tremolite amphibole fibers from widespread surface deposits may have a greater potential. The historical evidence is also strong, although subject to a certain degree of uncertainty over diagnosis. It is not that pathologists 50–100 years ago were less competent or discriminatory than they are today, but a few mistakes made when mesothelioma was rare or nonexistent would have a far greater impact on the question in hand than a similar number of diagnostic errors today when the disease is common.

The circumstantial evidence is by nature less conclusive. If mesothelioma in childhood is the same disease as that commonly seen in older men as a result of occupational asbestos exposure, it would strongly support the hypothesis. There is general consensus among pathologists that this is so. **The analyses of sex-specific incidence rates in relation to time or region are consistent in pointing to an annual rate of about 1 or 2 per million in both sexes at a time or place when the industrial use of asbestos could have had little influence. However, this evidence depends on extrapolation, an essentially speculative procedure.** The weakest evidence is undoubtedly that provided by lung burden analyses, depending as it does on failure to identify an etiological agent at death in a disease of very long latency.

In questions of this kind, analogous to those of cause and effect, certainty is not achievable. In a legal text, *proof* has been defined as "anything which serves immediately or mediately to convince the mind of the truth or falsehood of a fact or proposition." The eminent epidemiologist and statistician Bradford Hill advised the use of the following question: "Is there any other way of explaining the facts before us; is there any other answer equally, or more likely than cause and effect?" By these standards the evidence that there is and has been a background incidence of mesothelioma unrelated to the industrial exploitation of asbestos is quite convincing.

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THE MESOTHELIAL CELL AND MESOTHELIOMA

Edited by

Marie-Claude Jaurand

*Institut National de la Santé et de la Recherche Médicale
Crétail, France*

Jean Bignon

*University of Paris Val de Marne
Crétail, France*

*and
Institut National de la Santé
et de la Recherche Médicale*

Marcel Dekker, Inc.

New York • Basel • Hong Kong

Library of Congress Cataloging-in-Publication Data

The mesothelial cell and mesothelioma / edited by Marie-Claude Jaurand, Jean Bignon.

p. — cm. — (lung biology in health and disease : v. 78)

Includes bibliographical references and index.

ISBN 0-8247-9232-7 (alk. paper)

I. Mesothelioma. I. Jaurand, Marie-Claude. II. Bignon, Jean.

III. Series.

[DNLM: 1. Mesothelioma — physiopathology. W1 LU62 v. 78 1994 / QZ 340 M58005 1994]

RC280.L8M46 1994

616.99'2 — dc20

DNLM/DLC

for Library of Congress

94-16595

CIP

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Marcel Dekker, Inc.

270 Madison Avenue, New York, New York 10016

Current printing (last digit):

10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

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EXHIBIT 5

REVIEW

The epidemiology of mesothelioma in historical context

J.C. McDonald, A.D. McDonald

The epidemiology of mesothelioma in historical context. J.C. McDonald, A.D. McDonald. ©ERS Journals Ltd 1996.

ABSTRACT: Primary malignant mesothelial tumours were recognized by pathologists before asbestiform minerals (chrysotile, crocidolite and amosite) were mined commercially. The discovery, 40 yrs ago, of a causal link with crocidolite and the wide-ranging epidemiological studies which followed are the subject of this review.

Early case-control and descriptive surveys, supplemented by cohort studies in insulation workers and chrysotile miners, quickly demonstrated major occupational and geographical differences, with high risk in naval dockyard areas and in the heating trades. In the 1980s, reliable cohort surveys showed that in mining and in the manufacture of asbestos products the mesothelioma risk was much higher when exposure included crocidolite or amosite than chrysotile alone. However, qualitative and quantitative information on exposure was too often inadequate for this evidence to be conclusive. Well-controlled lung fibre analyses have reduced these deficiencies and demonstrated the probable implications of the greater biopersistence of amphibole fibres. Chrysotile for industrial use often contains low concentrations of fibrous tremolite, which may well explain the few cases of mesothelioma associated with this type of asbestos.

Progress in this field has been much retarded by controversy, for which the 20 year gap between the availability of reliable estimates of risk for the mining of chrysotile and that for crocidolite or amosite may have been largely responsible.

Eur Respir J., 1996, 9, 1932–1942.

Dept of Occupational and Environmental Medicine, National Heart & Lung Institute, Imperial College, London, UK.

Correspondence: J.C. McDonald
Dept of Occupational and Environmental Medicine
National Heart & Lung Institute
Imperial College
London
UK

Keywords: Amphiboles
biopersistence
chrysotile
lung analyses
mesothelioma
tremolite

Received: March 19 1995

Accepted after revision May 3 1996

A new industry, a new disease

Asbestos, the "magic mineral", was known to the ancient Egyptians and mentioned by Pliny, but only mined and manufactured in any quantity since about the 1890s. At that time, exploitation of large deposits of white asbestos (chrysotile) in Canada and Russia and blue asbestos (crocidolite) in South Africa began to develop rapidly. Early in this century, a brown asbestos, named amosite after the village of Amosa and the company which discovered it, together with deposits of chrysotile were also mined in South Africa. Crocidolite was later found and mined in Western Australia after the second world war and in lesser amounts elsewhere.

Primary malignant pleural tumours have been recognized at least since 1870, when WAGNER [1] published a report on a case of "tubercle-like" lymphadenoma of the pleura. In 1943, SACCONI and COBLENTZ [2], in a review of cases published before 1940, referred to the tumour as an "endothelioma", and mentioned a report by Lieutaud in 1767 of two such tumours in a series of 3,000 autopsies. They went on to say that, as knowledge of the tumour's existence spread, reports appeared with increasing frequency. These authors identified 41 cases in seven series published between 1910 and 1938 in a total of some 46,000 autopsies (0.9%), and added two cases of their own among 1,000 autopsies. The male to female ratio overall was 1.8, with 50% of subjects aged 40 yrs or more.

SACCONI and COBLENTZ [2] discussed the confusion which existed over pathology due, in their opinion, to the tumour's

rarity and lack of characteristic histology. From descriptions and photomicrographs of the 41 cases mentioned, they concluded that some at least were of other diseases, such as bronchogenic carcinoma. In view of diverging opinions at that time on the origin of cells lining serous cavities from which the tumour originated, they suggested that the name "pleuroma" be used. Later, however, the term "mesothelioma" became more generally accepted.

The link with asbestos

The suggestion that mesothelioma resulted from occupational exposure to asbestos was first made by GLOYNE [3], in Britain in 1935. In Germany, WEDLER [4] described two cases in men with asbestosis and WEISS [5] one case in a naval dockyard worker. LEICHER [6] was the first to report a case of peritoneal mesothelioma, in a textile spinner. At a scientific meeting in 1952, CARTIER [7], then in charge of the industrial medical clinic at Thetford Mines, Quebec, Canada, reported eight cases of respiratory cancer, two of which he described as pleural tumours. In his opinion, two such rare cancers in a small series of only eight cases suggested an occupational origin. A report in 1960 by WAGNER *et al.* [8] of 33 cases of mesothelioma mainly from the crocidolite-mining area in the north west Cape Province of South Africa put the association beyond reasonable doubt. Of the 33 cases, 28 were in persons who had worked in the mines or lived close to them. The pathological material available was limited to thoracic contents, and peritoneal tumours were not seen.

Table 1. – Early case-control studies of mesothelioma giving definite or probable occupational exposure to asbestos

First author	Year	[Ref.]	Place	Years diagnosed	Cases/controls	Male %	Occupationally exposed %	RR
ELMES	1965	[10]	Belfast, UK	1950–1964	42/42	95	76	3.6
NEWHOUSE	1965	[11]	London, UK	1917–1964	76/76	49	41	3.9
McEWEN	1970	[12]	Scotland, UK	1950–1967	80/80	91	58	4.2
McDONALD	1970	[13]	Canada	1960–1968	165/165	65	21	7.0
RUBINO	1972	[14]	Piedmont, Italy	1960–1970	50/50	64	12	6.0
ASHCROFT	1973	[15]	Tyneside, UK	1948–1967	27/56	88	93	2.3
HAIN	1974	[16]	Hamburg, Germany	1958–1968	150/150	71	58	6.3
ZIELHUIS	1975	[17]	The Netherlands	1969–1971	67/67	94	72	4.0

RR: relative risk; [Ref.]: reference number.

The 1964 New York Conference

At a conference on the "Biological Effects of Asbestos", a study by the Selikoff group of New York and New Jersey members of the International Association of Insulators and Asbestos Workers was a key event [9]. Of 632 males at work in 1942, 255 had died by 1962, three from pleural mesothelioma, and by 1964, 10 of 307 deaths were from mesothelioma - four pleural and six peritoneal. Two important case-control studies were also presented at this conference and later published (table 1). In the first of these, ELMES *et al.* [10] studied 42 cases of mesothelioma and 42 controls in Belfast, UK, matched for date, sex and age. Occupational histories were obtained from the living and from relatives of those who had died. Thirty six cases had a history of occupational exposure to asbestos, mainly in shipyards, compared with nine controls. The second study was by NEWHOUSE and THOMPSON [11] of 83 patients with mesothelioma diagnosed at a hospital close to the large Cape Asbestos factory in the east end of London, UK, which had opened in 1913. The control series comprised patients admitted later with other diseases, matched for sex and age. The authors acknowledged that neither these nor the interview methods were ideal but concluded that the case-control comparisons of occupational and residential histories were probably valid. Of 76 pairs, 18 cases (24%) had been employed at the asbestos factory and eight (11%) as insulators or ladders, compared with one (1%) and four (5%) controls, respectively. A further nine cases (12%) were in persons who had lived in the same house as an asbestos worker and were indirectly exposed, compared with one control (1%). Only crocidolite was used in the factory until 1926, when small quantities of chrysotile and amosite were introduced.

At the end of the 1964 conference, a Working Group under the auspices of the International Union against Cancer (UICC) reviewed the papers which had been presented and made a series of recommendations, with considerable emphasis on the need for more extensive epidemiological studies of mesothelioma and on the importance of asbestos fibre type [18]. As fibre of more than one type of asbestos was almost always used in manufacture it was suggested that research should concentrate on countries where it was mined or milled as the problem might then be less serious. Initially, this approach was taken only in the extensive chrysotile mines and mills of Quebec, Canada, and in the smaller chrysotile industry of northern Italy. Starting in 1966, all 30,000 current and previous employees of the Quebec industry

who had worked for at least one calendar month were listed. In addition to comprehensive studies of respiratory morbidity [19], mortality was investigated in a cohort of some 12,000 workers, born 1891–1920. Among 2,413 male deaths in the cohort to the end of 1966, there was a modest, exposure-related excess of lung cancer but only three deaths were from mesothelioma [20]. This prompted the need for studies of mesothelioma on a wider geographical scale. Almost 20 years passed before comparable studies were made in the production of crocidolite or amosite in South Africa and Australia, with a resulting controversy, which will be discussed at the end of this review.

Widening the epidemiological net

Case-control studies

From the end of 1967, all pathologists in Canada (over 400) were approached periodically concerning any fatal case of primary malignant mesothelial tumour diagnosed at autopsy or biopsy and, in 1972, the survey was extended to all pathologists (almost 7,000) throughout the USA. On each occasion, a response was obtained from nearly all of them [21]. The pathologists were then visited to discuss the diagnoses and to collect reports and material for panel review. A control with metastatic lung disease from a primary tumour outside the chest, matched for date, sex and age was selected from the same pathology file as the case. Relatives were interviewed, generally by a public health nurse ignorant of the case/control status, and detailed residential and occupational histories recorded. Jobs were coded blind, using a list classified by four different expert groups according to the probability of asbestos exposure.

Of 344 male cases of mesothelioma, 188 (55%) compared with 78 (23%) controls fell into one of the five defined exposure groups, presented in table 2. Insulation work - an infrequent occupation in controls - showed the highest relative risk (46.1). Asbestos production and manufacture was next in relative risk (6.1), almost wholly due to factory work. Employment in heating trades, shipyards and construction, after excluding insulation work, gave a lower combined risk (3.4). Occupational exposure to asbestos was recorded in only two of 162 female cases and no control. In three female cases and one control, exposure had been in the home to the clothing of a chrysotile production worker and in five cases and one

Table 2. — Case-control study of 344 male primary malignant mesothelial tumours of pleura and peritoneum, Canada 1960–1972, and USA 1972 [21]

Occupational group with definite or probable asbestos exposure	Cases (n=344)	Controls (n=344)	RR
A Insulation	27	1	46.1
B Asbestos production & manufacture (excl. A)	25	7	6.1
Mining and milling	4	2	
Manufacture	21	5	
C Heating trades (excl. A, B)	70	27	4.4
D Shipyards (excl. A, B, C)	21	13	2.8
E Construction (excl. A, B, C, D)	45	30	2.6
F Other (excl. A, B, C, D, E)	55	90	1.0
G None	101	176	1.0

RR: relative risk; excl.: excluding

control to that of an employee engaged in insulation or manufacture. Neighbourhood exposure was investigated by comparing the number of cases and controls who had lived within 20 miles of a chrysotile mine, excluding those occupationally or domestically exposed. No case with meso-thelioma but two controls had lived within 20 miles of a chrysotile mine in Quebec, Canada, and one case and two controls within 20 miles of a mine in California, USA.

Further evidence of an increased risk in shipyard areas was afforded by four of five other case-control studies published in the 1970s (table 1). Except for the report from northern Italy, where most of the occupational exposures were in or near Turin, shipyard exposures were mainly to blame.

Analyses of incidence and mortality

In the Canadian surveys described above, the annual incidence for 1960–1966 was one case per million persons - about 1.5 in males and 0.8 in females; however, there was probably under-reporting during these early years. In 1966–1972, the incidence in Canada was 2.9 per million males and 1.4 per million females; and in the USA in 1972, the corresponding rates were 2.7 and 0.8 per million. Cases in which a biopsy or autopsy specimen could be obtained were later reviewed by the Canadian and American mesothelioma panels of pathologists on a probability scale, first on histology, and then with clinical but not occupational information. In Canada, the incidence in Quebec was higher than that in Ontario, but fewer Quebec cases were accepted by the panel than for Ontario, and the corrected incidence in the two provinces was similar. These estimates were used in 1975 in a geographical analysis of all known cases of mesothelioma worldwide in areas where reported cases could be linked to population estimates. By applying age- and sex-specific rates found in Canada, the number of mesotheliomas expected on this basis was compared with the number observed. High ratios were found in many European shipyard cities, notably Walcheren, The Netherlands (23.3), Wilhelmshaven, Germany (21.5) and Plymouth, UK (14.3). In two locations with large asbestos manufacturing industries, there were also high ratios: Dresden, Germany (16.8) and the Manville-Somerville area of New Jersey, USA (26.5) [22].

It was evident that, even in the early 1970s, mesothelioma mortality in North America was already two or three times higher in males than females. This pattern became apparent in most industrialized countries and was followed by a steady upward trend in male mortality, which still continues. The implications of the much lower annual increase in females will be mentioned in a later section as evidence on the question of nonoccupational asbestos exposure. The steep rise in males, which probably began in the 1940s, is well explained as reflecting a parallel increase in the industrial use of asbestos, from about 1910, having taken account of a 30–40 year latency [23]. As a result of this increase, mesothelioma is currently responsible for some 20 deaths per million male population in Western Europe and North America compared with an estimated 1 to 2, 30–40 yrs ago. In early studies, only a minority of male cases were attributable to occupational exposure to asbestos, whereas, depending on location, up to 90% now are.

As the epidemic has evolved in the UK, the overall distribution of occupations which have been responsible has remained much the same but there is evidence that the contribution of work in shipyards has fallen but has increased in construction [24]. How long the mesothelioma epidemic can be expected to last is an important but difficult question. Estimated crudely from the industrial use of asbestos, it seemed possible that the peak might be reached in about year 2000; falling thereafter over a period of about 40 yrs [23]. Results of a recent and more sophisticated analysis of UK data are less optimistic and suggest that the peak may not be reached until 2010–2020 [25]. If true, this would point to the greatly increased importation of amosite for construction use in the UK during the 1960s and 1970s. However, these projections are highly dependent on the extent to which mesothelioma is better diagnosed and ascertained now than it used to be.

Other causal agents

Some 20 yrs after the pioneering work of WAGNER *et al.* [8] in South Africa, a discovery in some ways more dramatic was made by BARIS *et al.* [26] in Turkey. In some small villages in a circumscribed volcanic area of central Cappadocia, an extraordinarily high mortality from mesothelioma was observed in the local population. In Karain, a village of 575 inhabitants, in a 5 year period, 1970–1974, 24 from a total of 55 deaths were attributed to pleural mesothelioma. In Tuskoy, a larger village, both pleural and peritoneal tumours were in considerable excess. The rocks and soil of the affected area are rich in zeolite minerals, a common constituent of volcanic tuff. Erionite, a specific zeolite, was found in fibrous form in soil and rock samples and in respirable concentrations in both villages. Experimentally, these fibres are highly carcinogenic and readily produce mesothelial tumours in rats and mice [27]. The epidemiological investigations, although mainly descriptive rather than analytical, leave little doubt that these fibres are the cause of this unparalleled incidence of tumours in man [27]. Deposits of fibrous erionite are common in many areas of the world but to date there is no certain evidence, other than in Turkey, of an association with mesothelioma.

In a report from India, five cases of malignant mesothelioma were reported in sugar cane workers, with the suggestion that organic fibres might have been the cause [28]. Some support was obtained from Louisiana, USA, where two cases of mesothelioma were observed in similar circumstances [29]. In an electron microscopic study of ashed sugar cane leaf, silicon was found deposited along the hypoderm resulting in fibres 0.85 µm in diameter and 10–100 µm in length. The possibility that such "biogenic silica" fibres might be causally related to the tumour awaits further epidemiological study.

That mesothelioma might occur in workers exposed to man-made mineral fibres (MMMFs) was investigated in three large cohorts totalling some 41,185 workers employed in their manufacture in Europe and North America. Only four deaths were ascribed to the disease in a total of 7,862 deaths from all causes, one in a man also exposed to amosite [30]. Exposure levels in MMMF manufacture are extremely low, however.

Systematic cohort mortality studies

The 1980s saw the publication of results from a considerable number of cohort studies in specific occupational groups, which differed in industrial process and in

type of asbestos fibre to which the workers were exposed. The main and most recent findings from the more important of these investigations, classified by predominant industry, are summarized in three tables: mining and milling in table 3; manufacture of asbestos/cement products, asbestos textiles and asbestos friction products in table 4; and miscellaneous industrial groups in table 5. In a few of these studies, attempts were made to estimate exposure in terms of intensity and duration but in none could the level of exposure to individual fibre types be reliably assessed.

Mining and milling

The large cohort of chrysotile miners and millers in Quebec, Canada, first reported in 1971 has been followed ever since with updated results published periodically, the most recent in 1993 [31]. By this time, almost 80% of the cohort had died and the youngest survivors were in their mid 70s. From a total of over 8,000 deaths, 38 were probably due to mesothelioma - all pleural with one possible exception - a proportional mortality of just under 0.5%. A cohort of approximately one tenth the size from Balangero in northern Italy gave similar results. No comparable data on amphibole miners were available

Table 3. – Cohort mortality studies of male asbestos miners and millers*

First author	Year	[Ref.]	Country	Subjects n	Deaths		Deaths		Mesothelioma		Predominant fibre
					All causes n	%	Lung cancer n	SMR	n	PMR/1000	
MCDONALD	1993	[31]	Canada	10918	7312	67	545	1.33	33	4.5	Chrysotile
PIOLATTO	1990	[32]	Italy	952	427	45	22	1.11	2	4.7	Chrysotile
SLUIS-CREMER	1992	[33]	RSA (1) (2)	3212	648	20	26	1.38	4	6.2	Amosite
				3430	423	12	27	2.03	20	47.3	Crocidolite
ARMSTRONG	1988	[34]	Australia	6505	820	13	91	2.64	32	39.0	Crocidolite
MCDONALD	1986	[35]	USA	406	165	41	21	2.45	4	24.2	Tremolite

*: including vermiculite miners exposed to fibrous tremolite. [Ref.]: reference number; SMR: standardized mortality rate; PMR: proportional mortality rate.

Table 4. – Cohort mortality studies of male workers in asbestos manufacturing industries

First author	Year	[Ref.]	Country	Subjects n	Deaths		Deaths		Mesothelioma		Amphibole content
					All causes n	%	Lung cancer n	SMR	n	PMR/1000	
Asbestos-cement											
THOMAS	1982	[36]	UK	1592	351	22	24	0.93	2	3.5	Minimal
OHLSON	1985	[37]	Sweden	1176	220	19	11	1.23	0		
GARDNER	1986	[38]	UK	1510	384	25	35	0.92	1		
HUGHES	1986	[39]	USA (plant 1)	2565	477	19	48	1.17	2		
FINKELSTEIN	1984	[40]	Canada	535	108	20	26	4.80	19	20.7	Substantial
ALIES-PATIN	1985	[41]	France	1506	206	14	9	1.63	4		
HUGHES	1986	[39]	USA (plant 2)	4366	874	20	107	1.44	8		
MAGNANI	1987	[42]	Italy	2608	728	28	110	2.68	28		
RAFFN	1989	[43]	Denmark	7996	1305	16	162	1.80	13		
ALBIN	1990	[44]	Sweden	1929	592	31	35	2.50	13		
NEUBERGER	1990	[45]	Austria	2816	540	19	50	1.72	5		
Textiles											
MCDONALD	1983	[46]	USA	2543	570	22	59	2.0	1	2.5	Minimal
DEMENT	1994	[47]	USA	1247	607	49	72	2.25	2		
MCDONALD	1983	[48]	USA	4137	895	22	53	1.05	14	14.8	Substantial
PETO	1985	[49]	UK	3211	727	23	93	1.44	10		
Friction products											
MCDONALD	1984	[50]	USA	3641	803	22	73	1.49	0	0	Minimal
NEWHOUSE	1989	[51]	UK	9104	2055	23	229	1.03	11	5.4	Localized

For definitions see legend to table 3.

Table 5. – Cohort mortality studies of male and female asbestos-exposed workers in miscellaneous industries

First author	Year	[Ref.]	Country	Subjects n	Deaths						Predominant fibre
					All causes n	%	Lung cancer n	SMR	Mesothelioma n	PMR/1000	
Insulation work											
SELIKOFF	1979	[52]	USA & Canada	17,800	2271	13	397	4.24	175	77.1	Chrysotile & amosite
Insulation products manufacture											
SEIDMAN	1979	[53]	USA	unclear	528	-	76	5.78	14	26.5	Amosite
ACHESON	1984	[54]	UK	4280	333	8	38	1.31	5	15.0	Amosite
Filter assembly											
MCDONALD	1978	[55]	Canada	199	56	28	8	2.0	0	160.7	Crocidolite
JONES	1980	[56]	UK	1088	166	15	12	2.14	29	174.7	Crocidolite
TALCOTT	1989	[57]	USA	33	28	85	8	15.71	5	178.6	Crocidolite
ACHESON	1982	[58]	UK (a)	757	219	29	15	2.41	5	22.8	Crocidolite
			UK (b)	570	177	31	7	1.45	1*	5.6	Chrysotile
Dockyard work											
ROSSITER	1980	[59]	UK	6292	1043	17	84	0.84	31	29.7	Not stated*

*: also exposed to crocidolite. For definitions see legend to table 3.

until the late 1980s, when findings for crocidolite and amosite were published from South Africa and for crocidolite from Australia. At about the same time, two small cohorts of vermiculite miners in the USA, one of which had experienced substantial exposure to fibrous tremolite provided important evidence on its effects [35]. In interpreting the figures on proportional mortality in table 3, it should be noted that the crocidolite and amosite rates were derived from cohorts of which only 12–21% had died. At that stage in the evolution of the chrysotile cohorts, the proportional mortality from mesothelioma was less than 2 per 1,000. Proportional mortality rates are a very crude indicator of risk, since they do not take levels of exposure or competing causes of death into account. Nevertheless, the data in table 3 leave little doubt that crocidolite carries a much higher risk than chrysotile, with amosite and tremolite probably somewhere in between.

Manufacturing processes

The 17 cohorts shown in table 4 were informative in that all were engaged in the manufacture of asbestos-containing products, predominantly from chrysotile but some with the planned inclusion of relatively small quantities of crocidolite or amosite. Interpretation of the results is facilitated by the fact that the proportions dead at time of analysis in each cohort were of the same order, all but one (49%) ranging 14–31% (median 22%).

With each of the three types of product, there was a fairly consistent difference in the proportional rates for mortality from mesothelioma between cohorts with and without exposure to amphiboles. In cement workers, the relevant rates per 1,000 were 20.7 and 3.5, respectively; in textile workers 14.8 and 2.5; and in friction product workers 5.4 and 0. To these admittedly crude comparisons, made without reference to intensity or duration of exposure, some limited detail can be added. For example, the only death in the cohort of GARDNER *et al.* [38] was in a man first employed in the factory less than 7 years earlier. In the friction products cohort of NEWHOUSE and SULLIVAN [51], all but one of the 11 cases observed were from a small group of employees who worked for

a short time on a special crocidolite contract, and there was no case attributable only to chrysotile in the remainder of the cohort.

Miscellaneous occupations

Although all but one of the cohorts shown in table 5 were exposed wholly or largely to amosite or crocidolite, the data are of considerable interest. The very large cohort of American insulation workers investigated by SELIKOFF *et al.* [52] is one of the classic studies of asbestos epidemiology. At a stage when only 13% had died, almost 8% of deaths were attributed to mesothelioma, two thirds of which were peritoneal. Initially, it was thought that the exposure of these workers was mainly to chrysotile but it soon became clear that at least from 1930 onwards, amosite was the predominant type of asbestos used in American insulation materials. The suggestion was made at the Johannesburg Conference in 1977 that amosite rather than chrysotile might be responsible for the problem [60], but this has only recently been confirmed by lung burden analyses [61]. Two cohorts of workers exposed only to amosite in the manufacture of insulation materials, one in the USA [54] and the other in the UK [53], have provided further evidence of the capacity of this mineral fibre to cause mesothelioma. However, at face value, their levels of risk did not reach that of insulation workers employed in applying and removing these materials.

The highest recorded proportional mortality rates from mesothelioma were observed in two remarkable cohorts of males and females who worked for quite short periods of time during the early years of the second world war in England and in Canada on the installation of filter pads in military gas-masks. The pads were made from pure crocidolite believed to have come from the Wittenoom mine in Australia, where a cohort of miners and millers was studied some years later (table 3). An identical pattern in the incidence of cases began both in England and Canada 18 yrs after first exposure, and continued to grow for at least 10 more years; in the UK, new cases are still being seen almost 60 yrs later (J.S.P. Jones, personal communication). The nearest equivalent to these disastrous events was seen in a small group of employees in the manufacture of filters for cigarettes in the USA from,

of all things, crocidolite [57]. Five cases of mesothelioma from a total of 33 deaths (15%) were reported in that group.

Finally, a study by ROSSITER and COLES [59] of over 6,000 males employed in the Devonport (Plymouth, UK) naval dockyard is worth noting. Asbestos exposures were not well-documented but certainly included an appreciable proportion of crocidolite. This was not sufficient to produce excess mortality from lung cancer but it resulted in a large number of cases of mesothelioma.

Overview

Few, if any, environmental hazards have been the object of so many cohort studies as asbestos, only some of which have been mentioned in this review. Although it would be difficult to conclude from these data that the capacity of amphibole fibres, especially crocidolite, to produce mesothelioma is not considerably greater than that of chrysotile, uncertainties remain. The problem lies in the evident complexity of the causal relationships and the many factors other than fibre type with which the crude information available on exposure in these cohorts has failed to deal. Whilst duration of exposure can be estimated fairly accurately, fibre concentrations by size and type cannot. This is a serious problem when exposures are known to have been to more than one type of asbestos, and of increasing importance where one type is sometimes contaminated by another as, for example, chrysotile by tremolite or amosite by crocidolite. There is also reason to suspect that the nature of the industrial process may affect the outcome, as the textile industry does for lung cancer but not apparently for mesothelioma. It is, therefore, hardly surprising that, with the exception of the studies by HUGHES and WEILL [39] in the asbestos/cement industry, there still exist virtually no reliable data on exposure-response for mesothelioma which take account of any of these variables. To avoid the problems of environmental exposure assessment, more recent epidemiological research has turned increasingly to the use of lung fibre burden measurements. This approach and important new insights into the disease potential of chrysotile are discussed in a later section.

Nonoccupational mesothelioma

It is clear enough that in most cases of mesothelioma, particularly in industrialized countries, there is a fairly definite history of direct or indirect exposure to asbestos at work. This has led many to suggest that all cases may be caused in this way. This hypothesis raises two separate questions: firstly, is there evidence of a background incidence of the disease before, and presumably also since, asbestos was first exploited for industrial use? and, secondly, are there some cases attributable to asbestos but resulting from exposure in the domestic, neighbourhood or general environment rather than at work? These two aspects will be considered in turn.

The background hypothesis

In a recent review of this question [62], five types of evidence were examined, all of which pointed to the

probable occurrence of mesothelioma as a rare malignancy unrelated to asbestos exposure both before and since the industrial use of these fibrous minerals began at the end of the last century. The simplest evidence that cases are not all due to asbestos fibres is the high mortality from the disease in certain villages of central Turkey, to which reference has already been made. These cases were clearly caused by local deposits of fibrous erionite, a mineral with many physical and biological properties similar to crocidolite and tremolite. Deposits of fibrous erionite are widespread on the earth's surface and there is, indeed, some suggestion of related cases in proximity to deposits in the Rocky Mountain states of North America [63] but not elsewhere.

Other suggestive evidence, historical rather than geographic, has also been mentioned. It is fairly clear that primary malignant tumours of the pleura were recognized by pathologists at autopsy at the end of the last century, before the industrial use of asbestos could have been responsible and in the absence of any link with occupation. Although these cases were somewhat more common in males than females, their distribution suggests either a genetic aetiology or an environmental factor common to both sexes. The latter could conceivably include waterborne or airborne fibres originating from a wide range of naturally occurring minerals. The occurrence of mesothelioma in childhood leads to similar conclusions. Evidence of such cases was found in three surveys, the largest of which by FRAIRE *et al.* [64] recorded 80 cases in childhood, in only two of which was exposure to asbestos at all likely. Unless the usual latency with asbestos-related cases is much shorter in childhood, the existence of these cases suggests that there must have been some other cause.

Less conclusive support for a background incidence is afforded by the results of lung burden analyses in three case-control studies in North America and the UK, which are described more fully in the next section. In all three, a proportion of cases could not be attributed either to amphibole or chrysotile fibres. However, the small number of cases examined and the limits of fibre detection by electron microscopy reduce the confidence that can be put on negative findings.

More robust epidemiological evidence is given by mortality statistics for mesothelioma over the past 50 yrs or so. In most industrialized countries, the disease has increased much more rapidly in males than females, reflecting the impact of occupational asbestos exposure 30–40 yrs earlier. Backward extrapolation of these trends suggests that, before the diverging pattern began, mortality was about 1–2 per million population in both sexes. This conclusion is supported by data from countries or regions with low mesothelioma mortality, where both male and female rates are at about this level, and by data for California, USA, after exclusion of occupationally related cases [65].

If indeed there always has been a low background incidence of malignant mesothelial tumours unrelated to the industrial exploitation of asbestos, there remains the question of its aetiology. There are no indications that asbestos as it occurs naturally has been responsible, although this possibility would be difficult to refute. Similarly, although there are widespread deposits of other fibrous minerals, such as erionite and tremolite, which could conceivably

cause sporadic disease, there is very little evidence that they do. In special circumstances, however, where local rock has been used for domestic whitewash, as in New Caledonia and several Mediterranean countries [66–68], exposure to fibrous tremolite from childhood may well have led to a substantial number of cases. A number of other agents, such as biogenic silica fibre from burned-off sugar cane, some heavy metals (especially beryllium) and ionizing radiation have also been cited but none confirmed.

Neighbourhood and domestic exposure

The question thus comes down to whether the industrial use of asbestos - amphibole fibres in particular - can lead to sufficient environmental pollution outside the workplace to cause nonoccupational cases. It is fairly clear that such cases do occur, but rarely. The evidence is strongest in cases presumably resulting from domestic exposure among the household contacts of asbestos workers. Such cases were documented in several papers mentioned by GARDNER and SARACCI [69] in a recent review, in most of which crocidolite was probably responsible. The occurrence of neighbourhood cases has also been described in the immediate vicinity of crocidolite mines in South Africa and Australia [69], and of factories which used these fibres in London, UK, and Hamburg, Germany, [11, 16]. Most other studies of neighbourhood exposure have been negative.

More difficult to investigate is the possibility that cases of mesothelioma may arise as a result of general urban air pollution with asbestos fibres - almost all chrysotile and usually very short - in industrial cities of North America and Western Europe. There is little or no direct evidence one way or another for this hypothetical risk. That it is probably small and almost certainly beyond the limits of detection is suggested both by exposure-response findings in chrysotile miners and millers and by the fact that mortality in females in North America and Western Europe has shown little or no increase during the last 20–30 yrs. The latter holds despite the contribution of occupational and household exposure and the greater awareness by physicians and pathologists of mesothelioma during the same period [25].

Lung burden studies

Since the pioneering work of LANGER and POOLEY [70] in the early 1970s, the use of analytical transmission electron microscopy to identify and quantify mineral fibres in lung tissue has introduced a technique of great potential value for epidemiological research. In the assessment of past exposure, its specificity and cumulative capacity are far greater than was possible from work histories and scanty environmental measurements. On the other hand, this approach is limited in practice by the highly selected availability of lung tissue, and by the varied penetration, persistence and distribution of mineral fibres in the respiratory tract. Also, the significance of fibres in lung tissue at death is affected by whether or not the disease mechanism is related to these same fibre qualities.

It was shown by POOLEY [71] and ROWLANDS *et al.* [72] that there were substantial differences in the ability of

chrysotile and amphibole fibres to penetrate and persist in lung tissue. Thus, only studies which are adequately controlled for time variables and in other important respects, and where the analyses are conducted blind and in parallel, provide reliable information. The six surveys listed in table 6 are those in which these requirements were largely met, but even so with results which cannot readily be compared or tabulated.

Whilst it is evident from all six studies that amphibole fibres over 8 µm in length could have explained nearly all the cases and shorter fibres few if any, there are several arguments for and against the possibility that chrysotile may also have played some part. Certainly, the power of the multivariate analysis used by McDONALD *et al.* [77] was not sufficient to negate findings from their univariate analysis or to imply incompatibility with the observation by ROGERS *et al.* [78] of a chrysotile excess in the few cases where amphiboles were absent. In the latter study, the selection of all controls from a single hospital in Sydney, Australia, over a short period of time and the lack of matched pairs threw some doubt on the comparability of the 25 cases and 31 controls without amphiboles.

More substantial questions have been raised over the validity of conclusions on the role of chrysotile obtained from lung analyses at autopsy. Some have argued that only analyses of pleural tissue would have any relevance, perhaps without appreciating that the lung is simply being used in epidemiology as a sampling device to reflect past airborne exposure and not a direct pathological effect. The fact remains that as chrysotile is of low persistence, concentrations found at death may be unrelated to what was inhaled over a lifetime and, indeed, may predominantly reflect only very recent exposure. These questions have been reviewed by McDONALD [79], and more fully by CHURG [80]. In essence, the validity of lung burden measurements in epidemiology depends on: 1) how well they correlate with best estimates of past exposure; and 2) whether the investigations were controlled for time-related and other potentially confounding factors. For neither of these questions is the answer entirely clear. There is, indeed, evidence from a fairly small study by ROWLANDS *et al.* [72] and a larger one by SÉBASTIEN *et al.* [81] of a reasonably good correlation with past environmental exposure both for chrysotile and for tremolite in miners and millers in Quebec, Canada, and also in American textile workers, but further confirmation of this kind is needed. On the more difficult matter of adequate control for confounders, even among the six studies shown in table 6, not one was wholly adequate in this regard. It would seem unreasonable, even so, to reject entirely the consistent evidence which they present.

The association of fibrous tremolite with many chrysotile deposits, leading to low but varying contamination of the final product, was first identified by lung burden analysis in 1976 [71]. This discovery had two possible and conflicting implications: firstly, that these amphibole fibres might be disproportionately responsible for disease apparently due to chrysotile - particularly mesothelioma - but, secondly, that as a much more persistent fibre, it might simply serve as a marker of chrysotile no longer present. Before dismissing chrysotile as a cause of mesothelioma, therefore, note must be taken of the extent to which tremolite is found in lungs at autopsy in

Table 6. – Analysis of mineral fibres in lung tissue from mesothelioma cases and controls

First author	Year [Ref.]	Country	Cases	Controls	Odds ratio for amphibole fibres*	Evidence on chrysotile
JONES	1980 [73]	UK	86 cases notified by coroners & pathologists, 1976	56 cases (lung cancer 27, cerebrovascular disease 29); matched for age, sex & place	7.4	Chrysotile present in 2 of 4 cases without amphiboles
MCDONALD	1982 [74]	USA & Canada	99 cases from survey of pathologists	Secondary lung cancer; matched for age, sex, date and hospital	3.8	In pairs where amphibole content was $<10^6$ fibres·g ⁻¹ closely similar distributions of chrysotile
MOWE	1985 [75]	Norway	14 cases, county cancer registry, 1970–1979	28 cases excluding malignant and chronic pulmonary disease; matched for age, sex, year and residence	8.5 (based on all types of amphibole fibres)	Fibre type not identified
GAUDICHET	1988 [76]	France	20 cases from Nantes district, 1980–1982	20 each of adenocarcinoma and squamous carcinoma, secondary lung cancer and cardiovascular disease; matched for age, sex and hospital	amphibole fibre concentration 2–3 times higher than in controls	Similar concentration in cases and controls
MCDONALD	1989 [77]	Canada	78 cases from survey of pathologists, 1980–1984	Nonmalignant, nonrespiratory disease; matched for age, sex, date, hospital and type of sample	6.6 for fibres ≥ 8 μ m in length	Low level risk in univariate analysis and none in multivariate analysis
ROGERS	1991 [78]	Australia	221 cases from national surveillance, 1980–1985	359 tissue samples from a hospital in Sydney excluding nonmalignant respiratory disease and abdominal cancer; unmatched	16.6 for fibres ≥ 10 μ m in length	7 of 25 cases and 3 of 31 controls without amphibole fibres had $\geq 10^5$ fibres·g ⁻¹ chrysotile

*: calculated by ROGERS *et al.* [78], from comparison of cases and controls above and below 10^6 amphibole fibres·g⁻¹.

this disease. Light is thrown on this question by several studies, of which that by MCDONALD *et al.* [77], being well-controlled, indicated that of 78 cases of mesothelioma from across Canada, perhaps 29% were due to tremolite. An investigation in the USA by ROGGLI *et al.* [82], although without controls and therefore less interpretable in terms of cause and effect, identified tremolite fibres in unstated concentration in 55% of 94 cases. Thus, some of the mesothelioma cases apparently attributable to tremolite may have resulted from low-level contamination of industrial chrysotile, for which tremolite is not only a marker but, as shown below, may indeed be the cause. It must also be remembered that fibrous tremolite is a common contaminant of several industrially exploited minerals other than chrysotile.

The tremolite question

The extensive programme of epidemiological research in the mines and mills of Quebec, Canada, which began 30 yrs ago, was undertaken in the belief, wrong as it turned out, that the results would reflect exposure to pure chrysotile. Any impurities in the ore body were considered to be of minor importance and unlikely to cause difficulties in interpretation. The geological data available tended to support this view. The first indication that the situation might be more complicated was revealed by the results of electron microscope analyses of lung tissue from ex-mine workers reported by POOLEY in 1976 [71] and ROWLANDS *et al.* [72] in 1982. Not only did this show that chrysotile fibres were not alone but that amphibole fibres in the tremolite series were also present and usually in even higher concentration. In part, this reflected a lesser

ability of chrysotile to penetrate the smaller airways but the major factor was undoubtedly the greater durability of the amphibole fibres. Whatever the explanation, the possible importance of persistence in pathogenesis was immediately evident.

There are various reasons for taking this finding seriously in relation to mesothelioma. The most direct indication of the carcinogenic potency of mineral fibres in the tremolite series was seen in the small cohort of 406 Montana, USA, vermiculite miners and millers, results of which were published in 1986 (table 3). Among only 165 deaths, 21 were from lung cancer (standardized mortality rate (SMR) 2.45) and four from mesothelioma (proportional mortality rate (PMR) 24.2 per 1,000). At a comparable stage in the evolution of the chrysotile cohort in Quebec, Canada, among some 4,000 deaths, 10 were from mesothelioma (PMR 2.5 per 1,000). The average cumulative exposures experienced by the two cohorts were 145 fibres·mL⁻¹·yr⁻¹ in Montana and over 1,000 fibres·mL⁻¹·yr⁻¹ in Quebec. A very rough calculation would, therefore, suggest that if about 1% of the Quebec exposure was to tremolite, this amphibole fibre might explain the mesothelioma risk at both locations. At that time, however, there seemed to be no way in which this highly speculative hypothesis could be tested, let alone validated.

Further support for the general concept came to light a few years later in the case-control study based on lung tissue analyses of 78 mesothelioma deaths in Canada, 1980–1984 and matched referents [77]. Concentrations of amosite, crocidolite and tremolite, but not of chrysotile or any other identified mineral fibre, discriminated sharply between the two series. The attributable risk

associated with tremolite was estimated by multivariate analysis, suggesting that perhaps 23 of the 78 cases were due to tremolite, including all nine in the Quebec mining region. After excluding these cases, there remained 14 of 69 (*i.e.* about 20%) in the rest of Canada attributable to tremolite. Given that in the past crocidolite and amosite comprised less than 10% of all asbestos used commercially, it thus appeared possible that tremolite as a contaminant of chrysotile might explain most of the remaining cases.

A better opportunity to examine the hypothesis came a few years later when mortality in the Quebec cohort was updated [31]. By the end of 1988, 33 fatal cases of mesothelioma were identified in a total of 7,300 deaths from all causes (PMR 0.45 per 1,000) and by the end of 1992, 38 cases in a total of over 8,000 deaths (PMR 0.47 per 1,000). Among the 33 cases ascertained before 1989, 20 were from Thetford Mines, eight from the town of Asbestos, and five from a small asbestos products factory in Asbestos where crocidolite had also been used. Statistical analysis showed that the mesothelioma incidence was about 2.5 times greater among miners and millers at Thetford Mines than Asbestos [83]. Data on lung tissue analyses by Sébastien from our earlier survey [81], although scanty, showed that tremolite fibre concentrations were 2–4 times greater at Thetford Mines than Asbestos (ratio of medians 2.4; ratio of means 3.3) [83].

More demanding analyses are currently being applied to the most recent cohort data, focusing entirely on the 24 mesothelioma cases from Thetford Mines, 22 of which were in males employed by the largest company in that area. Advantage is being taken of two important facts: firstly, that this company had originally comprised many smaller companies distributed over a fairly wide geographical area; and, secondly, that lungs from 83 former cohort members from the same company had been analysed by electron microscopy for another purpose some 5 yrs earlier [81]. A preliminary analysis, now published [85] has demonstrated a remarkably close correlation between the high incidence of mesothelioma in a localized area of five mines and the concentration of tremolite fibre in the lungs of men who had worked in them [77]. These findings suggest that the relatively low risk of mesothelioma associated with chrysotile mining and milling may be largely determined by tremolite fibre contamination. Further analyses, which are now in progress, are needed to test this hypothesis and its wide implications.

Conclusion

After nearly 40 yrs of epidemiological research, the main determinants of malignant mesothelial tumours in man are reasonably clear. It could be said that this was apparent from the start, when WAGNER *et al.* [8] described a disease of long latency in workers who mined, milled and used crocidolite, and in their family contacts, but rarely in miners of other types of asbestos. Sadly, the picture soon became confused and our understanding clouded by controversy. It is worth considering the reasons for this.

A major factor was that, although it was evident from cohort studies of chrysotile miners and millers in the

early 1970s that this type of fibre rarely caused mesothelioma, it was nearly 20 yrs before comparable information became available for miners and millers of crocidolite or amosite. It is understandable that investigators familiar with the disastrous experience of insulation workers in North America, thought to have been exposed to chrysotile and possibly amosite, found it difficult to believe that all types of asbestos were not equally harmful. Their regrettable conclusion was that the data from Quebec, Canada, were wrong, or worse - a view supported by laboratory experiments which showed that all fibre types were equally carcinogenic for rats.

Against a background of suspicion and recrimination, the results of the several important cohort studies published in the 1980s failed to have much effect on entrenched and conflicting views. For those who saw chrysotile as a mineral fibre of low carcinogenicity, the findings summarized in tables 3, 4 and 5 confirmed this opinion. For those of the other persuasion, no great difficulty was found in maintaining their disbelief: the uncertainties associated with mixed exposures, lack of information on exposure intensity, and statistical chance were often cited, but less flattering reasons were not far below the surface. The aphorism that "what a man would like to be true, that he more readily believes" probably applied to both sides.

Some resolution of this unhelpful controversy came with the use of lung tissue analyses in epidemiological research. Despite difficulties in interpretation of results and the absolute need for properly selected controls [79], these studies have shown two things and are on the way to testing a third. Firstly, the clear evidence of an overwhelming predominance, with dose-response, of amphibole fibres in mesothelioma cases. Secondly, that amphibole fibres persist in lung tissue, whereas chrysotile does not; thus, the short lifespan of laboratory animals could not deal adequately with tumours with a characteristic latency of 30–40 yrs in men. Thirdly, the fact that it has been only by analysing lung tissue that the varying presence of fibrous tremolite has been demonstrated in chrysotile as produced commercially, and the growing probability that this previously unrecognized amphibole may be responsible for most cases of mesothelioma associated with heavy chrysotile exposures.

When peace finally returns to asbestos epidemiology, it may well be too late to restore chrysotile's soiled reputation. Like Caesar's wife, such materials must be beyond suspicion, and neither political nor administrative policies are easily reversed. The more important lessons from this saga probably relate to the screening and manufacture of asbestos substitutes - the man-made mineral and organic fibres. Given what we now know, it would surely be foolhardy, without extraordinary justification, to allow the widespread use of fibres which resemble crocidolite and tremolite physically and the amphiboles generally in their biological persistence.

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EXHIBIT 6

REVIEW

Mesothelioma: cases associated with non-occupational and low dose exposures

Gunnar Hillerdal

Abstract
Objectives—To estimate the importance of low dose exposure to asbestos on the risk of mesothelioma.
Methods—A review of the literature.
Results and conclusions—There is no evidence of a threshold level below which there is no risk of mesothelioma. Low level exposure more often than not contains peak concentrations which can be very high for short periods. There might exist a background level of mesothelioma occurring in the absence of exposure to asbestos, but there is no proof of this and this “natural level” is probably much lower than the 1–2/million/year which has been often cited.

(Occup Environ Med 1999;56:505–513)

Keywords: low exposure; asbestos; mesothelioma

Mesothelioma is an incurable disease which is almost exclusively due to inhalation of asbestos fibres. Asbestos has been extensively used in industry and construction in the 20th century, especially during and after the second world war, and even if the mineral is no longer used in most rich western countries the total world production remains high. There is a worldwide pollution with asbestos, as indicated by the finding of the mineral in samples of Greenland ice¹ and on the Yorkshire Moors,² and every citizen in the world has been exposed to some extent. Consequently, asbestos fibres can be found in most lungs at necropsy.³ It is thus understandable that there is concern about the risk of mesothelioma for the general population.

However, it should be remembered that mesothelioma is a rare disease with incidence in industrialised countries ranging from 1 to 5/million/year among women and values for

men 5–10 times higher (see table 3). Even in cohorts with a very heavy exposure to asbestos most people will die from other causes. In people with certified asbestosis—that is, with a heavy exposure—up to 10% will develop mesothelioma; among insulators in the United States and Canada, also a heavily exposed group, 9.3% of the deaths have been due to this disease; and in amphibole miners in South Africa or Australia, this figure is 2–4% (table 1). Clearly, with exposure concentrations several magnitudes lower, as occurs in the general population, the risk is very small, often impossible to measure.

A discussion of the risks from low exposure must include the dose-response curve; the existence or non-existence of a threshold, and thus a background concentration; and should try to define low exposure and estimate to what degree that really means a low concentration. From conflicting findings and opinions attempts must be made to make a meaningful conclusion.

The different types of asbestos seem to differ considerably in their ability to cause mesotheliomas. Chrysotile is considered by many authors to be a weak carcinogen in humans,¹¹ whereas the two amphiboles crocidolite and tremolite are much more dangerous according to many studies.¹² The third of the more important amphiboles, anthophyllite, was long considered not to cause mesothelioma, but such tumours have now been reported although the risk seems to be small.¹³ There is, none the less, a minority opinion that chrysotile is in fact responsible for most of the pleural mesotheliomas in society¹⁴ or should at least be considered to carry the same risk.¹⁵ This discussion, however, falls outside the present review and is not important for the conclusions drawn here.

Definition and diagnosis of mesothelioma
Mesotheliomas are, by definition, tumours that arise from mesothelial cells and can thus arise from any body cavity: the pleura, the peritoneum, the pericardial sac, and even the tunica vaginalis testis. Pleural mesotheliomas are the most common and pathologically the best defined ones. Pleural mesotheliomas have a male to female rate of about five to one, whereas for peritoneal tumours this ratio is 1.5 to 1.¹⁶ Thus, either the aetiology is different, the

Department of Lung Medicine, Karolinska Hospital, Stockholm, Sweden
G Hillerdal

Correspondence to:
Dr Gunnar Hillerdal,
Department of Lung Medicine, Karolinska Hospital, Stockholm, Sweden.

Accepted 8 March 1999

Table 1 Proportionate mortality from mesothelioma in various cohorts

Cohort	Deaths (n)	Deaths due to mesothelioma (%)	Reference
Amphibole miners	1225	2	4
Crocidolite miners	118	4	5
		6	6
Insulation workers	4951	9	7
Patients with asbestosis	283	9	8
	40	10	9
	59	10	10

Table 2 Possible risk factors and mediators of risk of mesothelioma (other than asbestos)

Factors	Comments	References
Erionite	Very high incidence of mesothelioma environmental exposure in Turkey	19
Chronic inflammation	Pleural scars (tuberculosis, pleurisy, therapeutic pneumothorax)	20
Radiation	Single cases after Thorotrast injection or radiotherapy; causality not proved	21 22
	One case in atomic bomb survivor	23
Beryllium	Two doubtful cases described	18
Vegetable fibres	No proof in humans	
Hereditary factors	Familial cases (explained by common asbestos exposure?)	24–26
	Correlation with parental cancer	27
Immunological factors	Rapidly progressive cases in patients with HIV infection	28 29
Dietary factors	Provitamin A, β -carotene may decrease the risk	30 31
Viruses	Mesotheliomas in animals	
	Simian virus 40 DNA sequences reported in mesotheliomas	32

diagnosis is more difficult in women, or women exposed to asbestos are more likely to develop a peritoneal than a pleural mesothelioma. In fact, one type of mesothelioma occurring almost exclusively in women is the so called multicystic mesothelioma. This tumour has a better prognosis, is more sensitive to cytostatic drugs, and seems to have no connection with exposure to asbestos.¹⁷

The pathological diagnosis of mesotheliomas requires experience, and confusion can occur with both benign pleural lesions and with metastatic pleural diseases.¹⁸ Many countries now have “mesothelioma panels”, which has meant a great improvement in the diagnosis. In most national cancer registries, most likely both overdiagnosis and underdiagnosis occur.

Suggested causes of mesothelioma other than mineral fibres

Apart from mineral fibres, radiation (for example, through the contrast medium Thorotrast) has been suggested to cause human mesothelioma. However, in a large retrospective study of more than 250 000 women treated for mammary carcinoma, a quarter of them initially with radiotherapy, no association between radiation and mesothelioma could be found.²² As can be seen from table 2, other causes or contributing factors have also been suggested.

Viruses can cause mesotheliomas in animals, but this has not been described in humans. DNA sequences associated with Simian virus 40 (SV 40) transforming factors have been reported in a high proportion of mesotheliomas from some countries.³² This suggests that there is a connection between SV40, which was a contaminant of live polio vaccines in 1959–61, and later development of mesothelioma. Thus, SV 40 might be a cofactor to asbestos in some patients with mesothelioma, but the results have not been confirmed and are still disputed.

In summary, then, as far as is known today, factors other than mineral fibres can only explain a very small proportion of mesotheliomas, and can for practical purposes be disregarded. Thus, a malignant mesothelioma can be regarded either as caused by asbestos or belonging to a normal background level—that is a spontaneously occurring tumour. The relative importance of these two factors has been debated and will be further explored in this review.

Incidence of mesothelioma

There is a large variation in the incidence of mesothelioma in different countries and in most places a steadily rising number of cases with time. In table 3, the incidence or mortality from mesotheliomas in different countries at various times can be seen. As mortality for practical purposes is the same as the incidence for this disease, both figures have been used in the table. Some of the differences between the countries are probably due to diagnostic difficulties, but most of the variations can be explained by the use of asbestos in the particular society some decades earlier.

Dose-response and latency time

Most researchers agree that there is a positive dose-response curve for mesothelioma—the heavier the exposure to asbestos, the greater the risk. This is found in cohort studies as well as in analyses of amphibole asbestos fibres in the lungs.^{45–48} It was realised early that time since first exposure was of great importance, and therefore the “cubic residence-time model” was suggested by Doll and Peto in their report in 1985⁴⁹:

$$I(T) = c \times F \times (T4 - (T-D)4)$$

Where, $I(T)$ =incidence at the time T after exposure; c =a constant depending on the process, F =intensity of exposure, and D =duration of exposure. This equation has been used in many studies with an acceptable fit for normal occupational exposure concentrations. F in the equation is the total exposure—a combination of fibre concentrations and exposure time—usually measured in fibre-years. (1 fibre-year = a mean of 1 fibre/ml air for 1 working year). Thus, the dose-response curve is supposed to be linear, but the result is heavily influenced by the time factor.

Unfortunately, the exact value of F is often uncertain, even in well defined highly exposed cohorts. The equation is thus rarely useful especially with low doses, in which F is usually a crude guess only. As can be seen from table 1, even with heavy exposure only up to 10% of a cohort will die from mesothelioma—so the formula is not applicable in these cases either. With very heavy exposure, most patients will die from pulmonary insufficiency due to asbestosis before there has been sufficient time to develop a mesothelioma.

Even more troublesome is the time factor T , which quickly becomes very important in this equation. If the equation is correct, the risk

Table 3 Incidence or mortality of mesothelioma in various countries and areas over time (/ million inhabitants / year)

Country or area	Year	Male	Female	Reference
United States	1968–81	2.1	0.8	33
North America	1972	2.8	0.7	34
Nantes-Saint-Nazaire, France	1956–74	5.2	0.2	35
Texas	1976–80	5.8	2.1	36
Selected cities, United States	1970s	4.4–11.1	1.2–3.8	37
United States	1986	7–13	1–2	38
Barcelona, Spain	1983–90	8.3	4.7	39
Great Britain	1968–71	8.4	2.3	40
Finland	1990–94	10	2.9	41
Great Britain	1972–76	12.6	2.8	40
Nantes-Saint-Nazaire, France	1975–84	17.2	0.8	35
United Kingdom	1983	17.5	3.2	16
Denmark	1978–80	14.7	7.0	42
Nantes-Saint-Nazaire, France	1985–92	19.4	4.0	35
Great Britain	1968–71	20.7	4.3	40
Australia	1982–88	28.3	3.3	43
Great Britain	1982–86	30.5	4.9	40
Great Britain	1987–91	44.0	6.4	40
Australia	1994	49.9	4.8	44

would increase steeply with time, making early childhood exposure of great importance.⁵⁰ However, there are clear indications that mineral fibres clear from the lung, albeit with different half lives for the different types of asbestos. Chrysotile has the shortest half life, and crocidolite is generally accepted to have the longest. The half life of crocidolite has been estimated to 7–8 years.⁵¹ This clearing of fibres would, at least theoretically, tend to actually decrease the risk of mesothelioma and other diseases with time.

In conclusion, the value of the cubic residence-time formula is in practice low and it should not be used for extrapolations, at least not at the extreme ends of exposure.

The latency time varies in different cohorts, and is dependent on how long a cohort is followed up. In 370 necropsy cases from Italy, latency time could be calculated in 312.⁵² Latency time was also dependent on exposure, varying from 29.6 years for insulators (with the highest exposure) to 51.7 in women with domestic exposure.

The threshold value and the background concentration

There have been strong arguments for the existence of a threshold value (a minimal exposure required for development of a mesothelioma).^{53–55} In most studies, several patients with mesothelioma do not report any occupational or other exposure to asbestos,^{33 56–60} and thus there seems to be a small spontaneous basal or background incidence of the tumour. In a large study from England, consisting of 185 cases and 159 controls who were very carefully interviewed, 5% of the cases (and 27% of the controls) seemed not to have any kind of exposure to asbestos.⁵⁹ This included domestic and even residential exposure. However, it is of course possible that some of these background cases might in fact be due to occupational, domestic, or even environmental exposure, unknown to (or forgotten by) the patients themselves.

There are authors who claim that the presumed background level must be very low, and retrospective searches for the tumour in the medical literature yield no convincing cases

of mesothelioma before 1946,⁶¹ although such negative evidence is of questionable value. McDonald and McDonald, in a recent review, estimated the background level to be 1–2/ million/year; they came to this figure by extrapolating backwards from epidemiological studies from various countries.⁶²

Malignant mesothelioma can occur in children,⁶³ and such cases can be considered as proof of non-asbestos (spontaneous) aetiology, as the latency time with necessity must be very short in these cases. Asbestos fibres have, however, been reported in the lungs of children, even in stillborn ones,^{64 65} showing that asbestos fibres spread in the human body and even penetrate through the placenta. Even if a latency time of only a few years is extremely rare in mesothelioma related to asbestos,⁴⁹ it can occur. There are some published examples of latency times of only 5 years.⁶⁶

Mesotheliomas also occur in animals, from baboons⁶⁷ and domestic dogs^{68–70} to fish.⁷¹ Dogs are exposed environmentally to asbestos just like their human masters, which might explain some of the tumours,^{68 69 72} but in fish it would be difficult to blame asbestos for the tumour. Thus, as in other animals, there is probably a background level of spontaneous mesotheliomas in humans.

Levels of exposure

Although many authors write about low level exposure to asbestos, there is rarely a definition of this term. In fact, in many articles low level exposure seems to be synonymous to non-occupational exposure, which, as described later, is certainly not true in many cases. Occupational as well as non-occupational exposure can be anything from very heavy to very low.

Occupational exposure to asbestos

It must be realised that occupational exposure to asbestos occurs or has occurred not only in the “classic” industries, such as asbestos mines and factories, shipyards, insulating business, asbestos cement industry, building and construction etc, but also in very many other occupations and trades. Examples are pulp and paper industry,⁷³ oil refineries,⁷⁴ electrical industry,⁷⁵ jewellery workers,⁷⁶ sugar refineries,⁷⁷ and cigarette filter workers.⁷⁸ Seamen and fishermen can have been exposed to asbestos used as insulation in their boats. In the reprocessed textile industry, bags heavily contaminated with asbestos could be reused for various other purposes, for instance covering heaps of rags; in an Italian investigation of such an industry, mesotheliomas and lung cancer were found to be fairly common among rag sorters.⁷⁹

Given the extensive use of the mineral, many people have been occupationally exposed to asbestos. This exposure can have been only brief but perhaps intense during that short period. In many or most instances the workers have no idea of the exposure and it can be impossible or almost impossible to elucidate it. Also, the level of exposure is often very difficult to estimate, should the information be available.

Non-occupational exposure to asbestos

DOMESTIC EXPOSURE

The family of an asbestos worker could be exposed to considerable amounts of asbestos brought home on his working clothes, which all too often it was the duty of the wife or daughter to clean. Pleural thickening, calcifications, and pulmonary fibrosis have been described in such cases, as well as mesotheliomas.⁸⁰⁻⁸²

AIR POLLUTION FROM ASBESTOS MINES, FACTORIES, DOCK YARDS, ETC

Asbestos mines used to be great environmental nuisances. They could be seen from a distance because of the dust cloud. Asbestos fibres can spread over a distance many kilometres from a mine, and the tailings from the mines were used for paving roads, parking areas, playgrounds, etc. In the crocidolite mining areas in South Africa, the incidence of mesotheliomas was increased to at least 10 times that expected even among women, proving a non-occupational exposure. However, whether some of this exposure was domestic (see later) is not clear.⁸³

Another example is the formerly active crocidolite mine at Wittenoom, Western Australia. At least 5000 people lived in the township of Wittenoom without working in the mines, and in 1993 27 cases of mesothelioma had occurred among these people.^{6 48 84} It has been estimated that 1.1% of child residents and 1.9% of the female residents of Wittenoom have died or will die from mesothelioma, whereas among the workforce this figure would be 6%.⁶

Around the chrysotile mines in Quebec, Canada, there have been at least 53 occupational mesotheliomas from the mines, nine domestic, and two with general environmental exposure only.⁸⁵ In the nearby towns, the lungs of residents who have never worked in the mines have a fibre concentration which is 10 times higher than that of the average Canadian.⁸⁶

Mesotheliomas have also been reported from the surroundings of asbestos factories⁸⁷ and in people living near dockyards. However, the risk from residential exposure is probably low. In a large study from England, this factor accounted for only 3% of all the identified cases.⁵⁹

CONSUMER GOODS

Asbestos has been introduced into various goods used by the public. Examples are wall paints and spackling and jointing compounds. Another is a hand held hair drier, of which 13 million were sold in the United States and which has been described as a "small asbestos spray gun".⁸⁸ In commercially produced Kent filter cigarettes, crocidolite was used in the filters from 1952–6. The sale of these cigarettes was 11.7 billion, and in the commercials the health effects of this filter was emphasised.^{78 89}

Once asbestos is introduced into a home, it will spread to all rooms and is almost impossible to remove even with a vacuum cleaner. It will easily be disturbed into the air from the slightest movement, and sedimentation is very slow.⁹⁰

URBAN AIR POLLUTION

The air in cities contains a very low concentration of asbestos. Near to construction or demolition work the concentrations are higher. It has been suggested that the air of London during the blitz was heavy with asbestos. Asbestos is also released on braking, and close to a motorway the fibre concentrations in the air will be higher than the background, but still well below the industrial threshold values. A risk not often appreciated is in dumps. In the vicinity of a waste disposal site the concentration of asbestos fibres can be 10–1000 times above the background concentration.⁹¹

Drinking water can contain asbestos or asbestiform fibres from natural sources or pollution. The use of asbestos cement pipes can cause a considerable number of fibres in the drinking water. Small amounts of asbestos can be found in some wines, beers, liquors, and other beverages, probably deriving from the filtration process. Fibres that are ingested will to some extent also enter the blood stream as seen from animal experiments.^{92 93} In humans, there are few reports. However, when amphibole fibres were found in drinking water from Lake Superior, a very small portion could be traced in urine,⁹⁴ and when chrysotile occurred in the drinking water, very small amounts were again found in urine.⁹⁵ However, most ingested mineral fibres will never be absorbed but will be cleared in the normal way, and the harmful effects of asbestos in drinking water or drinks is probably minuscule (and much smaller than the risk of drinking the alcohol).

Even if ingested asbestos is not dangerous, it has to be realised that it is only a very small portion of the tap water that we actually drink. Most of it is used for other purposes. Once the water has dried after washing, cleaning, taking showers etc the asbestos fibres will spread in the air. Such amounts are small but not insignificant and will add to the normal background exposure.⁹⁶

ASBESTOS IN PLACE = BUILDINGS CONTAINING ASBESTOS

A mixture containing asbestos was popular after the second world war for spraying on ceilings and walls for insulation and decoration. This was used well into the 1960s. There is now a public danger because of the plaster falling down from natural wear and tear, vandalism, or "artistic" carving in schools, etc. In many industrial buildings, asbestos was also used for spraying on the underside of the roof, and with natural wear and tear (and for instance birds building nests!)⁹⁷ there is now release of fibres to the surroundings. Asbestos was also extensively used in walls or around plumbing for insulation purposes, in cement to strengthen it, or just as a cheap filler.

In a modern city, asbestos can often be found in many places: in the cellar, where steam pipes are insulated; in storage or laundry rooms; in air conditioning sets; in theatres, museums, restaurants, etc.⁹⁸ Whenever there is damage to any construction or machine that contains asbestos, the possibilities of exposure, sometimes even fairly high, is there.

Table 4 Reported mesothelioma cases after exposure to “asbestos in place”

Occupation or exposure	Comments	Reference
School teachers	9/487 patients with mesothelioma 1 case each 4 cases	99 100–103 104
Attended school		102
Office clerk		102
Female office worker		105
Asbestos insulation at home	6/262 patients with mesothelioma	106

It has been claimed that up to 1000 premature deaths from lung cancer or mesothelioma will occur in the future among school children from schools where asbestos was used in the walls⁵⁰—calculations which, however, had to be built on extrapolations and assumptions. Several case reports have been published on patients with mesothelioma, in which the only exposure to asbestos that was reported was “in place” (table 4). From various cohorts with such exposure, significant increases in radiological findings from the lungs—such as pleural plaques—have also been reported, indicating exposure to asbestos, but these results are not undisputed and there is a probable overdiagnosis, as control groups are missing.¹⁰⁷

ENVIRONMENTAL MESOTHELIOMAS FROM LOCAL DEPOSITS OF FIBROUS MINERALS

“Endemic pleural plaques” were first described from Finland and since then many such findings have been reported. In these areas, there are small local pockets of asbestos which sometimes have been quarried, often for generations, for some local use. The most common use is whitewashing of houses with tremolite, which has resulted in an extremely high incidence of mesothelioma in some villages (table 5). When the exposure is due to whitewashing of the houses the risk will disappear when this procedure is stopped, but due to the long latency time this will take many decades.¹²²

A non-asbestos fibre, the zeolite erionite, has been found in some Turkish villages. Roads, buildings, etc, can contain this fibre in small amounts. Erionite is even more dangerous than crocidolite and the incidence of mesotheliomas in these unfortunate villages is extremely high.

Endemic plaques are of interest also in other countries, as many people born in these places and living there in their childhood and youth now have moved to other places, taking with them not only the plaques but also the risk of mesothelioma.¹³¹

Concentrations of exposure

OCCUPATIONAL CONCENTRATIONS

The concentration of exposure which the first workers exposed to asbestos have experienced can only be guessed. Estimated or recreated values from the past suggest fibre concentrations from 25 up to occasional values of 1000–2000 fibres/ml. With his own recalculations, Harries in 1970 estimated the fibre concentrations in the dockyard in 1951 as follows: sprayed asbestos insulation 171–322 fibres/cc; stripping asbestos 334; sweeping 353; adjacent passage 83; and in the passageway to the shower 25. Bagging debris 564; pipe lagging 194–200; removal of pipe lagging 171. Snap samples showed values up to 1000–2000 fibres/cc.¹³² These values are similar to the ones published by McMillan in 1983, who recreated values from the past: engine room 88; delagging in boilers room 171; bagging debris 353 f/ml.¹³³

Measurements from working places in the 1960s often showed peak doses of 20 fibres/ml and much less in more recent years. Where asbestos is still used, many countries have adopted a concentration of 1–2 fibres/ml as the upper legal concentration of exposure. These figures should be compared with the few available non-occupational measurements (table 6). A problem with the legal concentration is that most asbestos use today occurs in developing countries, many of which have adopted standards which they cannot enforce. As a result, actual exposures may be much higher than the standard in these countries.

NON-OCCUPATIONAL CONCENTRATIONS

The fibre concentrations in domestic exposure might in fact be as high as in occupational exposure. Brushing clothes might give peaks of ≥ 100 fibres/ml.⁵³ Ordinary vacuum cleaning is not effective in removing asbestos fibres, which

Table 5 Local deposits of mineral fibres (asbestos or erionite), occurrence of plaques, and of malignant mesothelioma

Country or area	Type of fibre	Plaques (% of investigated inhabitants)	Mesothelioma risk ($\times 10^6/y$)	Comment	Reference
Afghanistan	Tremolite	—	—	Case report only	108
Austria	Tremolite	5.3	Not increased	Vineyard and field workers	109 110
Bulgaria	Anthophyllite	2.8 women	Not increased	Tobacco growers	111 112
	Tremolite	5.6 men			
Corsica	Tremolite	41 (>50 y)	High	General pollution	113 114
Cyprus	Tremolite		High	General pollution	115
Czechoslovakia	Unknown	2.7–6.6	—	Farmers	116
Finland	Anthophyllite	6.5–9.0	Not increased		117 118
Greece:					
Metsovo	Tremolite	46.9	280	White washing houses	119–121
			140 (1985–94)		122
SW Aridea, Macedonia		24.2 (>40 y)	High		123
New Caledonia $\times 2$			8.3*	White washing houses	124
			300†		125
South Africa	Amosite crocidolite	2.5–6.6	High	Population around mine	4
Turkey	Tremolite	1.2–25	High	White washing houses	126–128
	Erionite	65		Farmers	19, 128, 129
USSR	Unknown	Locally high			130

*12 cases/145 000 inhabitants/10 y.

†Occurrence in local area.

Table 6 Fibre concentrations in air and lungs with non-occupational exposure to asbestos

Type of exposure	Fibres in air (f/ml)	Fibres in lungs ($\times 10^6$ /g dry tissue)	Reference
Domestic exposure (paraoccupational)		5.3–319.5 0.0049	11 102
Near asbestos mines, factories, etc:			
In Wittenoom:			48
When mine operating	0.5		
After closure of mine	0.01–0.21		
Farmers near mine in Canada		1.2–26.8	134
Local asbestos findings:			
Greece:			123
In the yard of an abandoned house	0.01		
In a newly whitewashed room	0.02–17.9		
Corsica	*	21 $\pm$ 11	114
New Caledonia:			
While sweeping floor	78		124, 125
Road dust clouds	0.06–0.67		
Asbestos in place:			
Teacher's aid		0.0043	102
Female office worker		31 (TEM)	103

*39 ng/m³ (100 times higher than controls). TEM = transmission electron microscopy.

can remain for years in the house and be airborne again whenever disturbed. Thus, domestic exposure is not low exposure.

Environmental concentrations in the villages where whitewashing occurs, low values are reported when there is no disturbance, but in a newly whitewashed room and while sweeping floors, the concentrations can be quite considerable (table 6).

With asbestos in place, as long as the asbestos is undisturbed the concentrations in the air are very low (zero or hardly measurable: ≤ 0.001 fibres/ml), but once deterioration takes place values can go up to 15 fibres/ml, and when being removed there can be even higher values. In schools in the United States, the mean concentration was estimated to be 0.003 fibres/ml, and in federal buildings 0.006.¹³⁵

Thus, with so called non-occupational exposure, the typical exposure is a low or very low, almost unmeasurable, background concentration, but occasional high exposure when there is a disturbance of some kind. It follows, firstly, that retrospective estimation of cumulative exposure from history alone is an impossibility in most cases; but secondly, and perhaps more importantly, that any person living or working in (or even temporarily visiting) buildings where asbestos has been used in construction or otherwise might well have been exposed to high concentrations of airborne asbestos fibres once or many times in their lives, and in most instances unknowingly. This includes most of us!

A better way of estimating lifelong exposure might be analysis of fibres in the lungs, but as already mentioned fibres do clear from the lungs. How big the differences in clearance are between people is unknown. Thus, the correlation between lifetime cumulative exposure and fibre concentrations in the lungs is not excellent, but the findings from the lungs probably give a better estimation of exposure than even a careful retrospective analysis of the patient's history, at least in low grade exposure. In most studies, there is a clear dose-response relation between exposure and the number of fibres in the lungs.^{11 12 46 48 51}

Fibres in the lungs of patients with non-occupational mesothelioma

As has been mentioned, asbestos fibres can be found in the lungs of the general population without any known exposure. In Germany, the upper normal limit was estimated to be 300 000 fibres/g dry lung. In a large study of 324 malignant mesotheliomas, from which 46 lung samples were available, it was found that even at a fibre concentration of 100 000–200 000 fibres/g, there was a fivefold increased risk of mesothelioma, which was significant.¹³⁶ In this study (which has unfortunately only been published in German) as in many others, the mean number of fibres in the lungs of patients with malignant mesothelioma is much higher than the normal values, but there are usually patients with values that lie within the normal level.^{25 137–141}

Discussion

Any asbestos fibre found in a lung must have been inhaled. As far as is known, no truly unexposed group can be found in the world. There is no proof of a threshold value—that is, a minimal lower limit below which asbestos fibres cannot cause the tumour—and thus it is plausible that even such low exposure can cause mesothelioma (even if the risk is extremely low). Patients with mesothelioma whose lungs show fibre concentrations within the normal range cannot be dismissed as background cases,—that is, not due to asbestos. The only way to prove such a hypothesis would be to compare the incidence of mesothelioma in a group with such background exposure with the incidence in a truly non-exposed group. This is not possible, as no such group can be found.

It is nevertheless possible that there is a background level of mesothelioma,—that is, that the tumour can occur even in the complete absence of asbestos (or erionite) fibres. However, the data reviewed here indicate that if so, this background level must be very low—probably much <1 case/million people/year. This figure comes from studies of industrialised countries, where background exposure to asbestos is unavoidable. What the true figure is can only be guessed.

What, then, are the consequences for the public health? From the studies of non-occupational exposures it seems probable that the occasional high level exposure situations are the ones that are most important. Although the background, hardly measurable, concentrations of fibres in the air cannot be completely dismissed, the cumulative risk of these exposures is probably minor—and what is more, there is no way to reduce these concentrations. It is the high concentration situations which should be avoided. By knowing where asbestos occurs, such risks could be identified. Any source of pollution by asbestos which releases significant amounts of fibres should be eliminated as soon as it is discovered, using correct equipment and techniques. Correct techniques are also necessary whenever rebuilding or tearing down of structures containing asbestos to avoid asbestos pollution of the environment. If

the asbestos is well contained and not disturbed, it is usually better to leave it in place. In many instances, encapsulation is also better than removal.¹⁴²

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EXHIBIT 7

BTS STATEMENT

BTS statement on malignant mesothelioma in the UK, 2007

British Thoracic Society Standards of Care Committee

The first British Thoracic Society (BTS) statement on mesothelioma was published in 2001 by a Working Party of the Standards of Care Committee of the BTS¹ in response to a request by the National Health Executive in England. In the last 5 years enough progress has been made to justify the preparation of a second statement. The most significant updates are in sections reviewing radiology and biopsy techniques and interpretation, the potential use of tumour markers, chemotherapy, radical treatment and the roles of the specialist nurse and multidisciplinary team approach in management. Recent major clinical trials are also reviewed.

As before, this updated statement was written by a Working Party of clinicians with an interest and experience in the disease with the aim of compiling a document to assist in the management of pleural and peritoneal malignant mesothelioma in the UK. We were again assisted by co-opted specialists, including radiologists, pathologists, nurses and oncologists, whose full details are given in Appendix 1. The draft was reviewed by the whole membership of the BTS and also sent to expert groups and patient representatives for whose comments we are grateful. Our statement is the result of this consultation process.

This statement is compiled primarily for clinicians who may be involved in caring for patients with mesothelioma and is based on literature searches and reviews by members of the Working Party responsible for particular sections. However, like its predecessor, it is not strictly evidence-based as we did not attempt a comprehensive review of all available literature. Moreover, in most aspects of this subject there are still no randomised trials on which to base guidelines. The management of mesothelioma remains subject to debate and variations in practice, so we have retained the term "statement" rather than "guidelines" in this revision.

This statement should be read in conjunction with the Mesothelioma Framework produced by the Department of Health's Lung Cancer and Mesothelioma Advisory Group.² The latter document is directed mainly at Strategic Health Authorities, cancer networks, primary care trusts and NHS trusts in England, and provides advice on how to organise mesothelioma services in order to improve standards of care to a uniformly high level.

EPIDEMIOLOGY

The incidence of mesothelioma in Great Britain has been increasing rapidly since cases began to be systematically recorded in the late 1960s when the mesothelioma register was established.³ Latest available projections of the future burden of the

Thorax 2007;**62**(Suppl II):ii1-ii19. doi: 10.1136/thx.2007.087619 disease in Britain suggest that the annual number of deaths will peak at between 1950 and 2450 deaths per year sometime between the years 2011 and 2015.⁴ The model suggests that for men in the highest risk birth cohorts—that is, those born in the late 1930s or early 1940s—mesothelioma may account for around 0.7% of all deaths. Although highly uncertain, long-range predictions suggest that around 65 000 deaths from mesothelioma may occur over the next 50 years. There is widespread variation in the incidence of malignant mesothelioma in England: two Strategic Health Authorities have <30 cases annually while two have >100 cases per year.²

Asbestos fibres are the cause of most cases of mesothelioma. Evidence from two British studies suggests that the proportion of men with mesothelioma directly attributable to occupational asbestos exposure may be about 85%,^{5,6} and this is consistent with evidence from studies in other countries.^{7,8} However, mesothelioma can also result from para-occupational exposures (for example, women who have laundered their husband's overalls) and non-industrial environmental exposures.⁶ Furthermore, there is some evidence to suggest that the rate of "spontaneous" mesotheliomas each year—that is, deaths which would have occurred even if the industrial exploitation of asbestos had never taken place—is around one per million or about 30 men and a similar number of women per year in Britain.

Mesothelioma can be induced by other non-asbestos fibres such as erionite found in rock in certain areas of Turkey.⁹ The suggestion that Simian virus 40 (SV40),¹⁰ which was found to contaminate polio vaccines administered in the 1950s and early 1960s in Great Britain, is a contributory factor has been refuted by recent studies.^{11,12}

The latency period between first exposure to asbestos and death from mesothelioma is typically very long. One review of over 20 epidemiological studies which documented latent periods reported a median latency of 32 years, very few cases with latency of <20 years and nearly one-third of cases with latency of >40 years.¹³ A more recent British study reported a mean latency of 41 years (range 15–67).⁵

Abbreviations: CALGB, Cancer and Leukaemia Group B; CT, computed tomography; EORTC, European Organisation for Research and Treatment of Cancer; EPP, extrapleural pneumonectomy; FDG, ¹⁸F-fluorodeoxyglucose; IIDB, industrial injuries disablement benefit; MARS, Mesothelioma And Radical Surgery; MRI, magnetic resonance imaging; PET, positron emission tomography; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumours; SMRP, soluble mesothelin-related proteins; SUV, standardised uptake value; VATS, video-assisted thoracic surgery

Correspondence to:
Dr John Wiggins, Wexham
Park Hospital, Slough SL2
4HL, UK; john.wiggins@
hwph-tr.nhs.uk

Received 20 July 2007
Accepted 13 August 2007

Summary of key points

- Malignant mesothelioma will increase in incidence over the next 5–10 years. It is inexorably progressive with a very poor 5-year survival and a median survival of 8–14 months.
- Malignant mesothelioma should be considered in any patient with either pleural fluid or pleural thickening, especially if chest pain is present. Prompt referral to a respiratory physician for further assessment is indicated.
- Where a chest radiograph is suggestive of malignant pleural disease, a copy report should ideally be sent to a designated member of the lung cancer multidisciplinary team, usually the chest physician, and preferably electronically or by fax.
- The pathological diagnosis of a diffuse malignant mesothelioma is not always straightforward and interpretation should always be taken in context with full knowledge of the clinical history, examination findings and radiological appearance.
- Where there is diagnostic uncertainty or where radical treatment is considered, cases should be referred to a specialist multidisciplinary team.
- An appropriately trained specialist nurse should be involved from the outset to support the care of the patient and liaise between hospital services, primary care and specialist palliative care services.
- The diagnosis should be communicated skilfully and sympathetically with a clear picture of the disease and the management plan. This information should be communicated to the general practitioner immediately.
- Written information about the disease, its medicolegal aspects and relevant organisations should be available to the patient and family.
- Early pleurodesis is a key aim for symptom control and prevention of the development of a trapped lung.
- Palliative radiotherapy provides pain relief in about half of all patients.
- All patients with mesothelioma and performance status 0–2 should have the opportunity to discuss the merits of chemotherapy with a specialist experienced in the use of chemotherapy for malignant mesothelioma.
- Supportive and palliative care aims to provide relief from pain and other physical symptoms and to respond to emotional, psychological, social and spiritual needs.
- Dyspnoea, cough and other symptoms should be managed according to palliative care guidelines.
- Radical surgery should, for the foreseeable future, only be considered within randomised trials such as MARS and MesoVATS.
- Peritoneal mesothelioma is related to asbestos exposure but is less common than pleural mesothelioma.

Analyses of the British Mesothelioma Register by occupational group and geographical area support the conclusion that the continuing increase in deaths from mesothelioma in Great Britain is a consequence of past occupational asbestos exposure.³ These analyses show that occupations and geographical areas with the highest mesothelioma risks tend to be

those clearly associated with heavy past asbestos exposures—for example, within industries such as shipbuilding, railway engineering, asbestos product manufacture and construction. However, analyses of trends in risk over time are consistent with the notion that deaths due to specific high-risk industries of the past are levelling off or falling more recently as other sources of exposure have developed over a wider range of occupations and geographical areas. Workers with the highest risks today are likely to be those subject to incidental exposures during the course of their work such as building maintenance workers; nevertheless, the lifetime risk for most individuals is extremely small.⁴

Measurements of airborne asbestos levels in buildings containing asbestos in good condition are typically several orders of magnitude below the lowest exposure levels seen in occupational cohorts of asbestos workers, and ambient asbestos levels in the general environment are likely to be even lower.⁶ Quantitative risk models derived from cohort studies may not be valid at these low levels, but they do indicate that substantial numbers of cases are unlikely to result from such exposures.^{13–14}

The risk of mesothelioma varies considerably in relation to the type of asbestos fibre, and there is evidence that the risks in relation to amphibole asbestos are considerably higher than chrysotile.¹⁵ Chrysotile was by far the most widely used type of asbestos in the UK. However, amosite was also used in substantial quantities and crocidolite to a lesser extent, as reflected in the figures on UK imports of the different asbestos types.¹⁶ Thus, many historical exposures are likely to have involved a mixture of fibre types, and the widespread use of chrysotile together with amphiboles in many asbestos products suggests that current exposures are likely to continue to do so.

Many thousands of workers have been exposed to asbestos fibres and have heard about the potential dangers, although only a small proportion will develop life-threatening disease as a result. These workers have justifiable anxiety about their future and may seek reassurance from the medical profession with routine chest radiographs. Although often requested by patients, annual radiographs of previously exposed individuals cannot be recommended. The current responsibilities of employers of workers who might be exposed to asbestos during the course of their work are laid out in the Control of Asbestos Regulations 2006 (Statutory Instrument 2006 No 2739).¹⁷ These Regulations describe the requirements for record keeping and medical surveillance, together with the actions to be taken if an employee is found to have a relevant disease.

The information now available about the risk of mesothelioma according to occupation, geographical area, birth cohorts and type of asbestos and age first exposed may allow advice about potential future risks in individual cases to be given in general and qualitative terms. Unfortunately, there is currently no basis for providing more specific advice to individuals.

CLINICAL FEATURES

Typically, presentation is either with chest pain, dyspnoea or both.^{18–19} The pain is usually dull, diffuse, occasionally pleuritic and characteristically worsens during the course of the illness. The pain may be described as heaviness or aching in the shoulder, arm, chest wall and upper abdomen. It sometimes has neuropathic components because of entrapment of intercostal thoracic, autonomic or brachial plexus nerves. Occasional patients are encountered who present with persistent chest wall pain with clear chest radiographs who develop either pleural masses or effusions during follow-up in the subsequent months. Cough may occur, particularly in patients presenting with a pleural effusion, but this is not usually a prominent symptom.

In the early stages, dyspnoea is usually caused by a pleural effusion but later may be due to the restrictive effects of pleural thickening. A chest wall mass, weight loss, abdominal pain and ascites (due to peritoneal involvement) are less common presentations. Profuse sweating may occur.

Occasionally the diagnosis is suspected following a routine chest radiograph. Pleural thickening or a mass may be visible on the chest radiograph after drainage of a presenting effusion and may prompt consideration of the diagnosis, as may the finding of other manifestations of asbestos exposure such as pleural plaques. Bilateral disease occurs rarely at presentation but is not uncommon in the terminal phases. A further uncommon but well-recognised presentation is with a pneumothorax.

Unlike carcinoma of the bronchus, presentation with cervical adenopathy, haemoptysis, non-metastatic syndromes and symptoms due to distant metastases is unusual. The disease is more likely to progress by local extension than haematogenous spread. Direct involvement of mediastinal structures is common, but hoarseness and superior vena caval obstruction only rarely cause major symptoms. Dysphagia, if it occurs, tends to be a pre-terminal event.

Sometimes patients present with acute pleuritic chest pain and a small effusion but initial investigations may fail to give a diagnosis. The patient may then remain symptom-free for many months until recurrence of the fluid or the development of chest pain leads to further investigation and ultimate diagnosis of mesothelioma.

Physical signs depend on the type of disease involvement and include signs of pleural thickening and effusion together with restriction of expansion of the hemithorax. Finger clubbing occurs more commonly in mesothelioma than in other forms of asbestos-related pleural disease.²⁰ Pericardial involvement may result in signs of tamponade. Weight loss may be prominent as the disease progresses.

Progression of the disease may be variable. Some patients have periods of apparent stability while others have relentless rapid deterioration.

Key points

- **Malignant mesothelioma should be considered in any patient with either pleural fluid or pleural thickening, especially if chest pain is present.**
- **It may occasionally present with persistent unexplained chest pain and a normal chest radiograph.**
- **Symptomatic metastatic disease is unusual at presentation.**

PROGNOSIS

Several studies have reported survival data, some measuring survival from date of onset of symptoms and others from date of definite diagnosis. A series reported from the UK showed an overall median survival from symptom onset of 14 months and confirmed a worse prognosis in those with sarcomatoid histology.⁵ A study of asbestos insulation workers in the USA showed that, among 141 cases of pleural mesothelioma, 36% died within 6 months, 64% within 12 months and 94% within 24 months of the onset of symptoms. Of 244 cases of peritoneal mesothelioma, 55% died within 6 months, 88% within 12 months and 98% within 24 months of onset of symptoms. In this series the median survival for pleural mesothelioma from onset of symptoms was 10 months and from diagnosis 5 months.²¹ The high number of patients with peritoneal mesothelioma is thought to reflect very heavy asbestos exposure in this group of workers. Survival data are difficult to interpret and compare because they vary in starting point.

Future studies should be based on date of acceptance of diagnosis by a multidisciplinary team.

There are prognostic factors that allow some refinement of prediction of life expectancy. Apart from non-epithelioid histology, the most important poor prognostic factors are male gender, advanced stage disease,^{22 23} poor performance status, leucocytosis and thrombocytosis. Several scoring systems such as the European Organisation for Research and Treatment of Cancer (EORTC) and Cancer and Leukaemia Group B (CALGB) have been used extensively in chemotherapy trials and have been validated as useful in estimating survival.

The few patients who survive >3 years are almost exclusively from the epithelioid group. Distant metastases occur commonly, although they are usually late and seldom cause problems. Yates *et al*⁵ reported their presence in >50% of cases at autopsy and with similar frequency in all histological types, although Law *et al*²³ found them more commonly in the sarcomatoid variety.

Key points

- **Median survival varies from 8 to 14 months in different studies.**
- **Survival should be measured from the date of acceptance of the diagnosis by a multidisciplinary team.**
- **The disease is inexorably progressive with a very poor 5-year survival.**
- **Epithelioid tumours have a better prognosis than other cell types.**

DIAGNOSIS

Diagnostic strategy

It is essential to use the combination of history, examination, radiology and pathology to reach a diagnosis of malignant mesothelioma. All the above elements are needed, and the overall strategy for diagnosis in a case of suspected mesothelioma is therefore to ensure that the patient has the relevant investigations rapidly and efficiently. In a clear-cut case it is possible to inform a patient of the diagnosis immediately a biopsy result is available, but in many cases it is usually wiser to defer this until the case has been discussed in detail at the local multidisciplinary team meeting and a diagnosis agreed. This also enables a preliminary view about management strategy to be given.

History

The history of asbestos exposure is very important but is often not recalled by the patient at presentation. An occupation may strongly suggest that exposure has occurred, although it is important to recognise less obvious occupations such as teacher, decorator and assembly worker. The possibility of neighbourhood or para-occupational exposure needs to be considered.

Further history at other stages of the patient's pathway is often much more informative after the patient has been able to think over his or her employment history. It has to be borne in mind that many patients will be attempting to recall working conditions up to 50 years earlier.

Physical examination

Physical examination does not usually aid the differential diagnosis. Occasionally tumour tissue may be felt between the ribs.

Investigations

Plain chest radiographic abnormalities may strongly suggest a malignant process. The key investigations subsequently are a pleural tap if an effusion is present and a contrast-enhanced CT

scan, together with an appropriate biopsy procedure²⁴ (see later sections).

A pleural tap can be performed in the outpatient clinic and the fluid should be sent for cytology and immunocytochemistry on a cell block. The risk of seeding from a pleural tap site is thought to be low, but the site of a puncture should be recorded.

If the clinical, radiological and cytological results subsequently support a diagnosis of mesothelioma, then this can be accepted. However, although immunocytochemistry can reliably show that cells are mesothelial in origin, it may be difficult to distinguish malignant from highly reactive cells. A biopsy is recommended if there is doubt about the diagnosis on radiological or clinical grounds as cytology may be unreliable.

In general medical practice it is not uncommon for a patient to have an undiagnosed pleural effusion despite a pleural tap and a CT scan. A potential diagnosis of mesothelioma may not have been considered by the managing team. For this reason, institutions are recommended to have a policy of prompt referral of such cases for a respiratory opinion.

A biopsy is required if the diagnosis is not clear after the pleural tap and a CT scan. The choices of technique are an ultrasound or CT-guided percutaneous pleural biopsy, or a thorascopic biopsy. Blind biopsy techniques are quick to perform and inexpensive, and are thus still used in some centres. However, a recent study has shown that a blind

Abrams’ punch biopsy is less effective at reaching a diagnosis for pleural thickening than a CT-guided biopsy, and the latter is therefore preferable.²⁵

Thoracoscopy is appropriate where there is pleural fluid and the technique facilitates not only complete drainage of the fluid and biopsy, but also immediate talc pleurodesis where appearances are clearly malignant. Where there is doubt about the macroscopic appearance, pleurodesis should be deferred. Biopsies are essential even if the appearances seem to be those of normal pleura.

The multidisciplinary team and the uncertain diagnosis

Sometimes, even after cytology, biopsy and a detailed multidisciplinary team discussion, there is uncertainty about the diagnosis of malignant mesothelioma. This may be strongly suspected but not diagnosable with certainty, and this uncertainty should be communicated to the patient even if he or she has to be managed with mesothelioma in mind. Occasionally, as indicated above, a diagnosis of malignant mesothelioma only emerges after time and repeated CT scans and/or biopsies. This strategy needs to be carefully explained to patients and their families. Most equivocal cases eventually turn out to have mesothelioma when indolent disease is accompanied by negative biopsies. Persistent effusions are unusual in the presence of benign pleural thickening. Difficult cases should be reviewed by a regional specialist

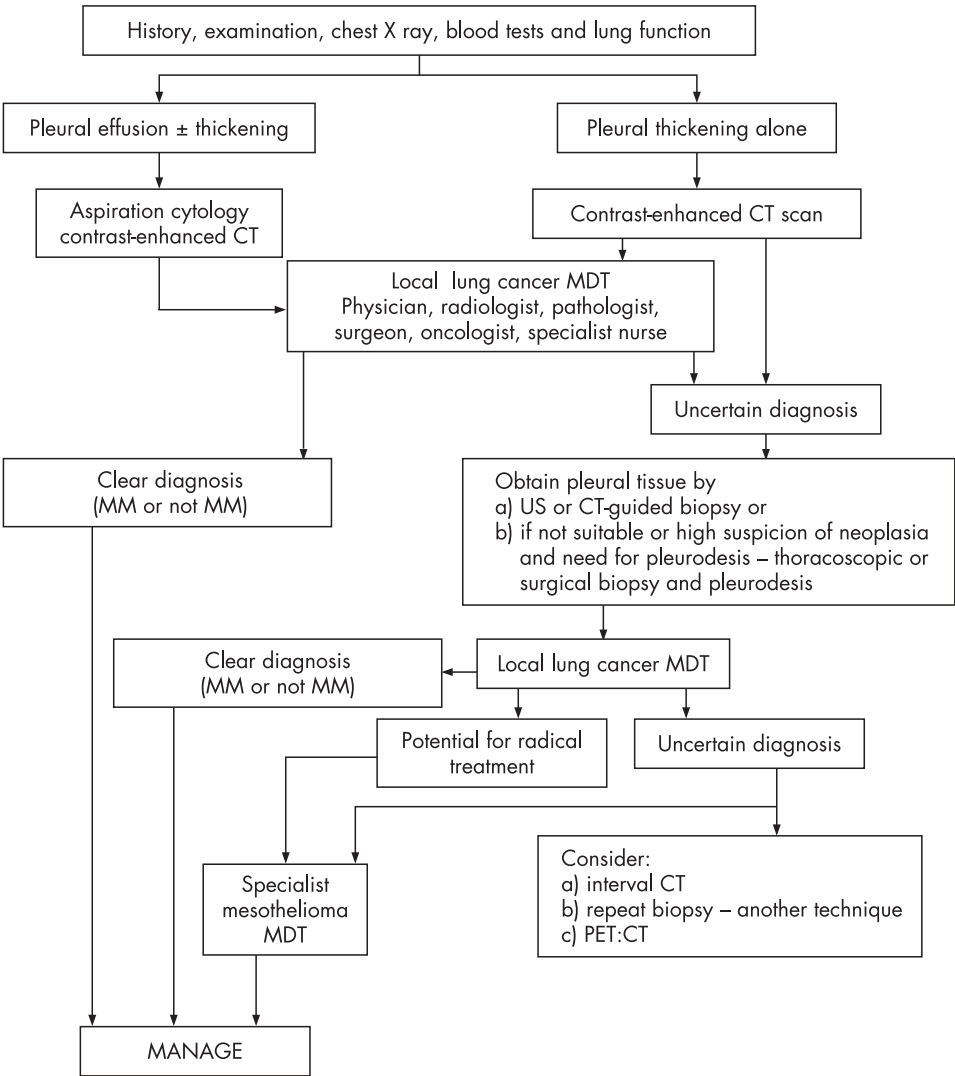


Figure 1 Suspected malignant mesothelioma: diagnostic algorithm. MM, malignant mesothelioma; CT, computed tomography of thorax; US, ultrasound; PET, positron emission tomography; MDT, multidisciplinary team meeting.

multidisciplinary team as recommended in the Department of Health Framework document.²

The points made in this section are summarised in the diagnostic algorithm shown in fig 1.

Key points

- **A detailed occupational history is essential.**
- **Any patient in whom mesothelioma is suspected should be promptly referred to a respiratory physician for further assessment.**
- **Pathological confirmation of the diagnosis is recommended unless the patient is frail or has extremely advanced disease.**
- **Negative pleural biopsy and cytological results do not exclude mesothelioma and should lead to further investigation or follow-up.**
- **CT scanning plays a key role in the diagnosis of mesothelioma.**
- **CT scanning, ultrasound and thorascopic biopsy are the preferred techniques for obtaining tissue.**

DIAGNOSTIC IMAGING

Imaging at presentation

The initial chest radiographic appearances of malignant mesothelioma may range from normal in early disease to complete opacification of a hemithorax, depending on the amount of pleural thickening and fluid present. The pleural thickening may manifest itself as discrete pleural nodules or may progressively encase the lung. The mediastinum may be either central or displaced. There should be a clear rapid referral mechanism in place if either a chest radiograph or a CT scan suggests malignant pleural disease.² A second copy of the radiologist's report should ideally be sent electronically or by facsimile to a designated member of the lung cancer multidisciplinary team, usually the chest physician.

Ultrasound can be very useful in identifying pleural abnormalities. The presence of a pleural effusion acts as an acoustic window, enabling the detection of intrapleural and intrapulmonary processes. Pleural effusions and thickening can be readily appreciated by ultrasound and discrete malignant nodules may be seen.²⁶ Ultrasound-guided biopsy of pleural thickening and drainage of effusions are well-established safe techniques.

Computed tomography (CT)

Contrast-enhanced CT is the primary imaging modality used for the evaluation of suspected malignant pleural disease. Malignant or inflammatory pleural disease enhances strongly, and the contrast allows differentiation between thickened pleura, effusion and underlying aerated or collapsed lung. Multi-detector CT allows a scan of the entire chest to be performed in <10 s. A scan delay of 60 s allows optimal visualisation of pleural disease while still allowing assessment of the mediastinal nodes and liver in the portal venous phase of enhancement. A standard protocol includes the liver and adrenal glands but should also include the lower abdomen and pelvis if there is a past history of malignancy in the abdomen or pelvis or clinical evidence of pelvic disease.

Leung *et al* studied 74 consecutive patients with diffuse pleural disease.²⁷ CT features used to distinguish malignant from benign pleural disease were (1) circumferential pleural thickening, (2) nodular pleural thickening, (3) parietal pleural thickening >1 cm, and (4) mediastinal pleural involvement. The specificities of these findings were 100%, 94%, 94% and 88%, respectively. The sensitivities were 41%, 51%, 36% and 56%, respectively. While the positive predictive value of these

signs is high, their absence does not exclude a diagnosis of pleural malignancy and CT cannot reliably differentiate malignant mesothelioma from other malignancy. Others have confirmed that the commonest features of malignant mesothelioma are circumferential nodular lung encasement, pleural thickening with irregular pleuropulmonary margins and pleural thickening with superimposed nodules.²⁸ These CT findings may be important for a working diagnosis in patients with poor performance status who do not want, or are unfit for, invasive biopsy procedures. Coincidental pleural plaques are found on the CT scan in approximately 20% of patients with malignant mesothelioma and there may be other features of asbestos exposure. Conversely, in many patients there may be no other radiological evidence of asbestos exposure. CT evidence of distant metastases is rare at presentation in malignant mesothelioma.

Magnetic resonance imaging (MRI)

MRI has a limited role in the evaluation of malignant mesothelioma. Pleural malignancy enhances avidly with use of gadolinium-based contrast material. Anatomical and morphological MRI features similar to those seen at CT are used to differentiate between benign and malignant disease and to establish local invasion.^{29–30} MRI, with its ability to scan in any plane, has been used to accurately assess resectability prior to radical surgery.³¹ Multi-detector CT scanning is able to provide detailed reconstructions, thus giving MRI only a limited role in evaluating patients with questionable areas of local tumour extension at CT or in whom intravenous administration of iodinated contrast material is contraindicated.

¹⁸F-fluorodeoxyglucose positron emission tomography (FDG PET)

In a limited number of patients where conventional imaging and biopsy have been either unhelpful or equivocal, FDG PET may be useful in differentiating benign from malignant pleural disease and might guide choice of biopsy site. Duysinx *et al* studied 63 patients with FDG PET and found this to have a sensitivity for detecting malignancy of 96.8% and a specificity of 88.5%.³² False positive results may be seen in cases of parapneumonic effusion and both tuberculous and uraemic pleural disease.³³ Care should be taken with patients who have previously undergone talc pleurodesis, as the inflammatory process caused by this procedure can also cause a false positive result.³⁴ It is not known how long the scan remains positive after pleurodesis.

The standardised uptake value (SUV) is used as a semi-quantitative measure of the metabolic activity of a lesion. The SUV is significantly higher in malignant mesothelioma than in benign pleural diseases such as inflammatory pleuritis and asbestos-related pleural plaques.³⁵ However, some cases of malignant mesothelioma are low-grade tumours and may not be avid on FDG PET. SUV can be taken at any time following injection of the tracer. There is neither an accepted time at which SUV should be measured in patients with malignant mesothelioma nor a particular threshold able to differentiate between benign and malignant disease. Volume measurements can be taken using SUV, and this offers the potential for assessing disease response following either chemotherapy or other novel treatment.

Imaging and staging

The TNM staging system proposed by the International Mesothelioma Interest Group (IMIG) is used for assessing patients with potentially resectable disease (see Appendix 2 available online at <http://thorax.bmj.com/supplemental>).³⁶ This staging system was designed as a surgical tool and may not be completely applicable to imaging. CT and MRI overall have

fairly similar accuracies for staging malignant mesothelioma, but both techniques may underestimate the stage of the disease.³⁷ Although both techniques have been shown to be sensitive in predicting resectability,³⁸ CT is routinely used in view of its speed of examination and availability. Radiological staging may be required for entry into a clinical trial.

Mediastinal nodes are commonly involved by mesothelioma and, as with the staging of lung cancer, CT has limited accuracy for detecting mediastinal node involvement. FDG PET also appears to be relatively poor at distinguishing mediastinal nodal metastases from adjacent mediastinal pleural involvement, although a high SUV seems to correlate with the presence of N2 disease.³⁹ Co-registration of CT with PET images, “CT-PET”, may have a role in assessing these patients but studies are limited at present.⁴⁰ Currently, mediastinoscopy is normally performed before radical surgery to exclude patients with N2 disease. CT-PET may have a complementary role aiming to detect occult metastatic or N3 disease.

Imaging and assessment of disease response

The assessment of disease response is important in evaluating treatment in both everyday clinical practice and clinical trials. Solid organ tumours are normally measured with either bidimensional⁴¹ or unidimensional measurements. Response Evaluation Criteria in Solid Tumours (RECIST)⁴² is based on the assumption that tumours are generally spherical, and that a maximal unidimensional measurement correlates well with an overall reduction in tumour size. Malignant mesothelioma tends to grow as a rind around the chest wall, and changes in tumour bulk tend to manifest as changes in tumour thickness perpendicular to the chest wall rather than the maximal tumour dimension. Studies have shown discrepancies between tumour measurement in malignant mesothelioma using the World Health Organisation (WHO) and RECIST criteria.⁴³ The RECIST criteria have now been modified and validated with particular reference to malignant mesothelioma.⁴⁴ Semi-automated three-dimensional measurements have been described but are not routinely used.⁴⁵ Difficulties arise in patients who have undergone pleurodesis as this causes an inflammatory response and subsequent pleural thickening. If the patient is to undergo chemotherapy following pleurodesis or surgical decortication, a baseline scan should be performed immediately before this.

Key points

- Where a chest radiograph is suggestive of malignant pleural disease, a copy report should ideally be sent to a designated member of the lung cancer multidisciplinary team, usually the chest physician, and preferably electronically or by fax.
- The multidisciplinary team should have a mechanism in place to follow up these reports.
- In patients with suspected malignant pleural disease, a chest CT scan should be performed before pleural biopsy or thoracoscopy.
- CT scanning cannot reliably differentiate malignant mesothelioma from other causes of malignant pleural disease.
- Ultrasound-guided pleural aspiration should be used as a safe and accurate method of obtaining fluid if the effusion is small or loculated.
- MRI has a limited role in patients with malignant mesothelioma (over and above multi-detector CT).
- PET scanning may be useful in differentiating benign from malignant disease but further studies are needed.

- Radiological staging of patients with malignant mesothelioma should occur before radical surgery and before clinical trial entry.

PATHOLOGY

Pathological diagnosis may be obtained from cytology or histology. Cytological diagnosis is based either on sampling of effusion fluid or by percutaneous fine needle aspiration cytology of a region of pleural thickening. In specialist centres the sensitivity of the former technique can be up to 76% and the latter 78%.⁴⁶ Immunocytochemistry can be applied to the cytological material (including cell blocks), which can fairly reliably identify that the cellular content is mesothelial. However, where there is poor clinical and radiological correlation, the pathological diagnosis should be based on tissue biopsy due to difficulties in distinguishing malignant mesothelioma cells from reactive mesothelial cells and other pleural malignancies in fluid.^{47 48}

Percutaneous core biopsy may provide sufficient material on which to confirm a diagnosis of malignant mesothelioma and to perform ancillary studies. This is reported to have a higher yield (86% sensitivity and 100% specificity) than closed Abrams’ or Cope needle biopsy which only offers a sensitivity of 21–43%.⁴⁹ Others have shown a sensitivity for needle biopsy of 60% with a single attempt and 85% with repeat biopsies.⁵⁰ Thoracoscopy has a sensitivity of over 90% with a low complication rate (10%).⁵¹

Separation of benign from malignant mesothelial proliferations

Establishing the nature of the mesothelial proliferation present in a sample is one of the most challenging aspects of diagnosis. The US-Canadian Mesothelioma Reference Panel have produced guidance in this area.⁵² It recommends a conservative approach, with equivocal cases being labelled “atypical mesothelial hyperplasia” or similar and, if appropriate, further tissue sampled.

Pathologists should be prepared to submit samples for expert review in cases of diagnostic difficulty.

Histopathological classification

The precise cell of origin of malignant mesothelioma is unclear, but it is now suggested that tumours arise from submesothelial cells that have the ability to differentiate along diverse lines. Numerous histopathological subtypes of diffuse malignant mesothelioma have been described (table 1). It is important for the pathologist to be aware of these alternative forms but the WHO classification advises that, as these various subtypes have no particular prognostic significance, tumours should be classified into one of three main types: epithelioid, sarcomatoid (with desmoplastic mesothelioma being a particularly

Table 1 Varieties of diffuse malignant mesothelioma (main types shown in bold type)

Epithelial	Sarcomatoid
Tubulopapillary	Fibrosarcomatoid
Solid variant	Chondrosarcomatoid
Adenomatoid	Osteosarcomatoid
Small cell	Leiomyosarcomatoid
Clear cell	Malignant fibrous histiocytoma-like
Deciduoid	Lymphohistiocytoid
Adenoidcystic	Desmoplastic
Pleomorphic	Biphasic (= mixed)
Mucin-positive	Any combination across the above groups

Table 2 Histochemical and immunohistochemical methods used to differentiate mesothelioma from adenocarcinoma

	Epithelioid mesothelioma	Adenocarcinoma
Histochemistry		
PAS	+ (glycogen)	+ (small amount of glycogen with mucin)
plus diastase	– (almost always)	+
Alcian blue		May be +
plus hyaluronidase	+	Usually still +
Immunohistochemistry	–	
Calretinin	+	–
CK5/6	+	–
WT-1	+	–
Thrombomodulin	+	–
HBME-1	+	–
N-cadherin	+	–
CEA	–	+
MOC-31	–	+
Ber EP4	–	+
B72.3	–	+
LeuM1 (CD15)	–	+
E-cadherin	–	+
Lewis (BG8)	–	+
TTF-1	–	+ (lung and thyroid)
Others	Either	Or

Note that all may give aberrant or unexpected results occasionally and need to be assessed in combination, and also that adenocarcinomas from non-pulmonary sites may show different expression (for sensitivities and specificities see King *et al*⁵³ and Ordóñez⁵⁴).

aggressive form of the latter) and biphasic. Classification into these three main groups is important as it may alter management.

Ancillary tests

Despite the numerous publications describing the usual morphological features of mesothelioma, confirmation requires support from additional studies which may include histochemical, immunohistochemical and electron microscopic analysis. Unfortunately, no single stain or test can unequivocally confirm or exclude a diagnosis of mesothelioma and a panel of tests are performed, particularly when trying to differentiate mesothelioma from adenocarcinoma.

Epithelioid mesotheliomas can mimic (and be mimicked by) several other tumours, most frequently metastatic adenocarcinoma. The most useful differentiating histochemical stains are those for mucins (table 2). Two recent publications have reviewed the immunohistochemical profile of mesotheliomas compared with metastatic adenocarcinoma, which most commonly spreads from the lung.^{53 54} These confirm that a panel of antibodies is required and the most useful are listed in table 2. Most pathologists employ a limited combination of these markers with a mixture of positive and negative results indicating the diagnosis.

Immunohistochemistry is useful in differentiating between reactive and neoplastic mesothelial proliferations, particularly in cytological preparations or superficial biopsies. EMA is more likely to be positive in a neoplastic process, with more extensive p53 expression, while desmin decorates reactive mesothelial cells preferentially.⁵⁵ The usual markers, however, are of much less value when trying to confirm the diagnosis of sarcomatoid malignant mesothelioma, where the sensitivity and specificity is much lower.⁵⁶

Immunohistochemistry is useful in differentiating mesotheliomas from tumours other than adenocarcinoma (whether primary or metastatic). Table 3 lists most of the important differential diagnoses of diffuse malignant mesothelioma with antibodies that may aid diagnosis.

Electron microscopy can play a role in the diagnosis by demonstrating the long slender microvilli of mesotheliomas that contrast with the broader, blunt microvilli of adenocarcinomas.

Specific types of mesothelial tumour
Well-differentiated papillary mesothelioma

This is a rare tumour (fewer than 50 cases in the world literature) that deserves mention because of its confusing name and more indolent course and prolonged survival. Asbestos exposure has been reported in some cases of this tumour, but a genuine epidemiological association has not been established. It can be either localised or diffuse, and is more commonly found in the peritoneum of women. However, cases in the pleura are recognised (where the sex bias is less obvious).⁵⁷

The typical microscopic appearance is of broad fibrovascular cores covered by a single layer of bland mesothelial cells. There are no mitoses and invasion of the underlying stroma is not seen. If this diagnosis is made pathologically but the disease proves to be rapidly progressive, then the correct diagnosis is probably a diffuse epithelioid malignant mesothelioma and further tissue sampling is indicated.

Multicystic mesothelial proliferation

This is a multicystic proliferation of mesothelial cells which has previously been considered by some to be a reactive process and by others a benign neoplasm. It is most frequently seen in the abdomen of premenopausal women and is sometimes associated with previous surgery or endometriosis. It is characterised by multiple fluid-filled cysts lined by flattened mesothelial cells. It is now clear that the condition can also be found both in the pleura and in men. It invariably has a benign clinical course.

Solitary fibrous tumour (localised fibrous tumour/ mesothelioma)

This is an uncommon spindle cell neoplasm that occurs most frequently in the chest but which can occur in virtually any site in the body; it should not be confused with localised malignant mesothelioma⁵⁸ which is a localised form of the diffuse tumour described above. Solitary fibrous tumour characteristically arises from the visceral pleura, is well circumscribed and may be pedunculated. The microscopic hallmark is a bland spindle cell proliferation arranged in a “patternless pattern”. The cellularity is variable with cellular areas interspersed with hypocellular collagenised regions. Vessels are usually prominent. Tumour can be infiltrative and cells are usually positive for CD34 and bcl-2 while cytokeratin antibodies are almost always negative. These tumours generally are benign, although occasionally malignant behaviour is recognised. The malignant varieties tend to cellularity, cellular atypia and high mitotic activity (>4 per 10 high power fields). Approximately 15% of cases have hypertrophic pulmonary osteoarthropathy and 15% have recurrent hypoglycaemia.

Key points

- The pathological diagnosis of a diffuse malignant mesothelioma is not always straightforward and interpretation should always be taken in context with full knowledge of the clinical history, examination findings and radiological appearance.
- Pleural fluid cytology and histology of blind biopsy specimens have a low diagnostic yield for mesothelioma but are important initial steps in differential diagnosis.
- Pathologists should attempt to specify the histological type of mesothelioma.

Table 3 Differential diagnosis of diffuse malignant mesothelioma

Differential diagnosis	Immunohistochemistry that may help
<i>Primary pleural tumours</i>	
Angiosarcoma	CD34, CD31, FVIIIIR
Epithelioid haemangioendothelioma	CD34, CD31, FVIIIIR
Synovial sarcoma	Cytokeratins, CD99, bcl-2, cytogenetics
Sarcomas (various)	Various depending on type
Localised malignant mesothelioma	None
Solitary fibrous tumour	CD34, bcl-2, CD99
Well-differentiated papillary mesothelioma	None (needs macroscopic appearance and usually peritoneum)
Adenomatoid tumour	None (needs macroscopic appearance)
Calcifying tumour of the pleura	None (usually young patient)
Desmoplastic small round cell tumour	Cytokeratins, desmin, EMA, WT-1, NSE
Thymic tumours	Cytokeratins, EMA, occasionally CD5
Lymphoma	Lymphoid markers
<i>Metastatic tumours</i>	
Carcinomas	Cytokeratins
Sarcomas	Various depending on type
Lymphomas	Lymphoid markers
Malignant melanoma	S-100, HMB45, melan-A
Thymic tumours	Cytokeratins, EMA, occasionally CD5
<i>Non-neoplastic mimics</i>	
Pleural fibrosis	Rarely cytokeratins
Reactive mesothelial cells	Desmin, EMA, p53

- **A selection of special stains must be used to confirm mesothelial origin of a tumour and aid differentiation from other pleural neoplasia.**
- **Pathologists should be prepared to submit samples for expert opinion in cases of diagnostic difficulty.**

Role of serum markers in diagnosis

Two recent studies have described the use of serum markers in the diagnosis of malignant mesothelioma. Osteopontin is a bone-derived glycoprotein that is overexpressed in a number of malignancies including lung, breast, gastrointestinal tract and ovarian tumours. In patients with malignant mesothelioma, serum levels were raised in comparison with both healthy subjects and asbestos-exposed controls. The levels in exposed individuals with pleural plaques with pulmonary fibrosis were raised, but not to the same extent as those measured in patients with malignant mesothelioma. Using a cut-off value of 48 ng/ml, the assay had a sensitivity of 78% and a specificity of 85%.⁵⁹ Soluble mesothelin-related proteins (SMRP) are thought to be involved in cell adhesion and its monoclonal antibody binds to normal mesothelial cells, mesotheliomas and some ovarian cancers. Raised SMRP levels were found in 37 of 44 individuals with malignant mesothelioma (sensitivity 84%) and only 3 of 160 patients with fibrosis, benign pleural disease and non-mesothelioma cancers. Seven of 40 individuals with asbestos exposure had raised SMRP levels, and 3 of these apparently disease-free individuals subsequently developed malignant mesothelioma.⁶⁰ Epithelioid tumours were more likely to be associated with raised SMRP levels, and the levels appeared to correlate with tumour size and fell following surgical debulking. A recent larger prospective multicentre study⁶¹ confirmed higher levels of SMRP in malignant mesothelioma in comparison with both other malignancies with pleural involvement and benign asbestos pleural disease; however, the test was less sensitive than initially reported when distinguishing pleural metastasis from malignant mesothelioma (58%). There was a

clearer distinction when SMRP was measured in pleural fluid and the levels tended to be considerably higher.

Diagnosis at an early stage of the disease should, in theory, improve prognosis and identify patients for whom radical treatment might be indicated. The rate of false positives in exposed healthy individuals must cause concern and would engender considerable anxiety in a cohort of exposed men who, in all likelihood, will never develop malignant mesothelioma. Before large-scale screening with tumour markers can be recommended, prospective studies will be required to confirm sensitivity and specificity of the test, the natural history of an individual with an increased level of the marker and, ideally, demonstrate an impact of the measurement on mortality. Meanwhile, data on SMRP might be studied prospectively as part of treatment trials. As yet, SMRP is not widely available commercially; however, a markedly increased level in an appropriate clinical context might increase diagnostic confidence in cases where tissue diagnosis is equivocal.

Cytogenetics may play a part in diagnosis in the future but at present is not routinely used as no single alteration or pattern of alterations is diagnostic.

MANAGEMENT

General management

Patients with mesothelioma should be discussed by a lung cancer and mesothelioma multidisciplinary team, be under the care of a specialist (usually a respiratory physician) and have a specialist nurse allocated to them. The multidisciplinary team should include core professionals as defined in the National Institute for Health and Clinical Excellence (NICE) guidelines and Department of Health Framework document. Where there is diagnostic difficulty or a possibility of radical treatment, the patient should be discussed at a specialist multidisciplinary team meeting.

The specialist nurse (usually a lung cancer or mesothelioma specialist nurse) should facilitate the pathway of care for the patient and the family throughout the illness, ensure good liaison between hospital services and primary care, and ensure access to specialist palliative care services as required. Patients should be advised who to contact in case of need. Further details are provided in a later section.

The diagnosis should be communicated skilfully and sympathetically. A clear picture of the disease and what to expect, including a realistic prognosis, should be given to the patient and, if appropriate, to families and carers. It is important to avoid a nihilistic approach. A copy record of the consultation could be offered to the patient. Immediate communication with the general practitioner should include the known extent of the disease, what was said to the patient and the management plan.⁶²

Ongoing follow-up by a member of the multidisciplinary team (usually the respiratory physician) is recommended, even if there is no change in treatment, as it provides an opportunity for further discussion including issues of compensation and benefits, symptom control and provision of support. There should be continuing close liaison with the general practitioner and primary health care team. The patient should have access to a specialist nurse, usually the nominated key worker.

The relatives or carers and the general practitioner should be warned, at an appropriate stage, that a Coroner's post mortem examination will nearly always be required after the death of a patient with mesothelioma, and all deaths have to be reported to the Coroner (in Scotland the Procurator Fiscal).

Key points

- **A patient with mesothelioma should be discussed at a multidisciplinary team meeting and be under the care of a specialist.**

- **Where there is diagnostic uncertainty or where radical treatment is considered, cases should be referred to a specialist multidisciplinary team.**
- **An appropriately trained specialist nurse should be involved from the outset to support the care of the patient and liaise between hospital services, primary care and specialist palliative care services.**
- **The diagnosis should be communicated skilfully and sympathetically with a clear picture of the disease and the management plan. This information should be communicated immediately to the general practitioner.**
- **Written information about the disease, its medicolegal aspects and relevant organisations should be available to the patient and family.**
- **Assessment of psychological, social and spiritual needs of patient and family/carers should be undertaken at key points during the disease pathway. Information should be offered about appropriate support services.**
- **The general practitioner should be reminded that all deaths have to be reported to the Coroner (in Scotland the Procurator Fiscal); an inquest is usually required.**

Treatment strategy

Essential management points to be considered on diagnosis are:

- Management of the pleural effusion.
- Indications for prophylactic radiotherapy to intervention sites.
- Indications for chemotherapy.
- Immediate supportive care requirements.
- Compensation issues.
- Suitability for radical surgery.
- Suitability for clinical trial entry.
- Referral to the specialist multidisciplinary team.

Organisation of care

This is discussed in detail in the Mesothelioma Framework document.² The difficulties facing patients with malignant mesothelioma are diagnosis, palliation, allocation to a specialist treatment (eg, surgery), recruitment into randomised trials and obtaining advice about social, financial and legal issues. For these reasons, every patient has a right to have his or her disease considered by an experienced team with a declared interest in this cancer. The essential composition of such a team is a chest physician, a radiologist, a pathologist, a surgeon, an oncologist and a cancer nurse, all with expertise and an expressed interest in the disease. The team should have ready access to specialist palliative care services and opinions. If local services cannot meet these criteria, we consider it advisable that arrangements are made for the routine referral of patients with malignant mesothelioma to a team with the required attributes (the specialist multidisciplinary team). Such referrals could be managed by record review, teleconferencing or by attendance at a clinic, depending on individual circumstances. Ongoing care should continue to be with the local team if it is in the patient's best interest. We recommend that initially a network of identified cancer nurses with expertise in malignant mesothelioma is established to facilitate such referrals at a local level.

There is no evidence to support the contention that the management of a given number of cases of malignant mesothelioma per year provides evidence of expertise, either in individuals or a multidisciplinary team. An expressed and

evident special interest may be more important, although we consider that teams diagnosing fewer than 10–15 cases per year are unlikely to develop and retain the attributes required. A typical specialist multidisciplinary team would be expected to discuss a minimum of 25 cases annually.²

Surgery

The role of surgical resection in malignant mesothelioma is very uncertain. Two approaches can be taken. The more radical is extrapleural pneumonectomy (EPP) (sometimes referred to as pleuropneumonectomy). The less radical approach is a debulking operation (sometimes known as cytoreductive surgery), which is either performed at open thoracotomy or by video-assisted thoracic surgery (VATS). Both are being tested in randomised controlled trials (see below). Radical treatment should only be considered for patients with epithelioid tumours (although the Mesothelioma And Radical Surgery (MARS) trial has not made this distinction owing to unreliability of sampling techniques).

Extrapleural pneumonectomy (EPP)

This procedure was first described in the 1970s⁶³ and its aim is to eradicate all macroscopic disease, ideally with good clearance margins. The nature, extent, pattern of growth and proximity to major organs makes mesothelioma impossible to eradicate completely without resection of all the parietal and visceral pleura, the underlying lung, the diaphragm and the pericardium. Even then there are often doubts about resection margins. Operative mortality is 4–9%,⁶⁴ but significant complications from EPP occurs in over 60% of patients.^{63–67} A median survival of 19 months following this radical operation with adjuvant chemotherapy and radiotherapy has been reported in the largest series, but this is based on highly selected patients reported with no indication of the denominator from which they were drawn and no control or comparative group.⁶⁸ There have been further series reporting “improved” outcomes following EPP with multi-modality therapy, but again with no control group.^{69–74}

The absence of randomised controlled trials on the role of EPP for mesothelioma led a recent systematic review of surgical management to conclude that the role of EPP could not be defined.⁷⁵ Currently, the MARS trial is recruiting in the British Isles in its pilot phase. This is a randomised study comparing EPP against no EPP surgery within the context of trimodality therapy (neoadjuvant chemotherapy and postoperative radical hemithoracic radiotherapy). The aim is to randomise 50 patients to determine the feasibility and acceptability of performing an adequately powered randomised trial. The primary outcomes of the main trial will be survival and quality of life. Patients being considered for EPP should be treated within the context of the MARS trial.

With potentially high mortality and morbidity, patients must undergo rigorous preoperative assessment before being considered for EPP. Fitness for surgery should be assessed according to standard BTS guidelines for pneumonectomy in lung cancer⁷⁶ and should also include preoperative echocardiography to assess pulmonary artery systolic pressure.

Preoperative staging with a CT scan, PET scan and mediastinoscopy are important to assess resectability (T1–3, N0–1, M0). Together with positive resection margins and non-epithelioid subtypes, involvement of mediastinal lymph nodes has been shown to be a negative predictor of survival following EPP.^{69–77} A PET scan, particularly integrated CT-PET imaging, identifies distant metastasis⁷⁸ but is less good at identifying positive N2 lymph nodes owing to the proximity of the mediastinal pleura. Accurate staging of the mediastinum by mediastinoscopy is therefore required in the MARS trial in all

patients for whom randomisation is being considered for possible EPP.

As most patients who present are usually already in advanced stages of the disease, only a minority may be eligible for EPP. Of these, it is likely that only a few will benefit from radical treatment with or without EPP. Until there is clear evidence for EPP, it cannot be recommended as the treatment of choice.

Debulking/cytoreductive surgery

This less radical approach, which can be performed by VATS or thoracotomy, involves removal of as much of the tumour burden as possible without removing the underlying lung, diaphragm or pericardium. Where the underlying lung is trapped by the diseased pleura, re-expansion of the lung may be possible following decortication,⁷⁹ thereby offering symptom control with less morbidity.⁸⁰ VATS pleurectomy/cytoreductive surgery has been reported to be effective in preventing fluid recurrence⁸¹ and may also be associated with increased survival⁸² although, like EPP, it has not yet been tested in a randomised trial.

MesoVATS is an ongoing randomised study in the UK comparing VATS cytoreductive surgery against bedside talc pleurodesis in patients with a pleural effusion secondary to proven or suspected mesothelioma. Survival and quality of life are outcome measures, as well as clinical and cost effectiveness. Patients who present with a pleural effusion and have been deemed ineligible for the MARS trial should be considered for the MesoVATS trial.

Patients referred for radical surgery should be aware that it is likely to be either preceded or followed by chemotherapy and followed by hemithorax radiotherapy ("trimodality therapy"). Patients should be given realistic information about the perioperative risks and the chances of long-term survival.

Key points

- **There are no randomised control trials to establish the role of radical surgery.**
- **Radical surgery should only be considered within a randomised trial.**
- **Surgery should be concentrated in centres where there is experience in performing extrapleural pneumonectomies.**
- **The present claims for benefit are for surgery within multimodality therapy.**
- **Patients should be aware of the potential for trimodality treatment and be given realistic information about outcomes.**

Management of pleural effusion

One of the central aims in the management of patients with symptomatic pleural effusions caused by mesothelioma is to achieve an early and successful pleurodesis. This helps symptom control and a trapped lung is less likely to occur if the procedure is performed promptly. Given the low diagnostic yield of bedside procedures, early thoracoscopy also gives an opportunity to obtain a definitive histological diagnosis.

Thoracoscopy⁸²⁻⁸⁶ is an extremely useful technique in the evaluation and management of undiagnosed exudative pleural effusions. As well as providing a high diagnostic yield, it allows complete drainage of the pleural space followed by talc poudrage. Thoracoscopy can be performed under conscious sedation (usual for medical thoracoscopy) or under general anaesthesia (VATS). Complications are uncommon but include pleural space infection and surgical emphysema.

If the patient is either too frail to undergo thoracoscopy or a firm diagnosis has already been made, talc slurry pleurodesis

may be performed via an intercostal drain.^{87 88} Occasionally, simple repeated pleural aspirations without pleurodesis may be appropriate for very frail patients with advanced disease. Small-bore indwelling catheters and drainage systems are an alternative in these circumstances.

Chemical pleurodesis should be performed via a small bore (16–18F) that should be flushed regularly with normal saline to maintain its patency.⁸⁹ Lignocaine (3 mg/kg; maximum 250 mg) should be administered intrapleurally just before sclerosant administration. In addition, premedication should be considered to alleviate anxiety and pain associated with pleurodesis. Satisfactory apposition of the parietal and visceral pleura should be confirmed radiographically. There are no data to suggest that suction improves the success rate,⁸⁹ or that frequently changing the position of the patient improves either dispersion of the sclerosant or the success of pleurodesis.^{90 91}

Currently the most effective freely available pleurodesis agent is sterile talc.^{88 89 92 93} The dose of the talc should not exceed 4 g, and it should be calibrated to avoid the rare risk of the development of adult respiratory distress syndrome.⁹⁴ The intercostal tube should be clamped for 1 h after sclerosant administration and, in the absence of excessive fluid drainage (>250 ml/day), removed 24–48 h later. Recent data showed no difference in success rates between talc poudrage and talc slurry.⁹⁴

Pleuroperitoneal shunts have been used where pleurodesis has failed and for trapped lung. However, there is a high complication rate, including shunt occlusion and infection. Their use is therefore diminishing.⁹⁵

Unfortunately, a minority of patients will have a trapped lung at presentation or develop the problem during the course of their disease. If asymptomatic, partial entrapment and little fluid production then no action is required. However, if there are symptoms due to rapid re-accumulation of pleural fluid, an indwelling pleural catheter may be inserted. Catheters may be inserted as day case procedures and, with nursing support, allow patients and their carers to drain their effusions at home. They have been shown to significantly improve the quality of life⁹⁶ and, with regular drainage, up to 45% of effusions undergo spontaneous pleurodesis.⁹⁷ Complications are rare but include pleural infection.^{96 97}

None of the available techniques designed to control pleural effusion in malignant mesothelioma is universally successful. Patients and their carers should therefore be made aware of the risk of re-accumulation of pleural fluid and the methods of accessing the secondary care team—for example, via the cancer nurse specialist.

Key points

- **Early pleurodesis is a key aim for symptom control and prevention of the development of a trapped lung.**
- **Thoracoscopy is an extremely useful diagnostic and therapeutic tool.**
- **Calibrated talc is the pleurodesis agent of choice.**
- **Indwelling pleural catheters are useful for symptom control in cases of trapped lung or where chemical pleurodesis has failed.**

Radiotherapy

Radical radiotherapy as a single modality

Irradiation of the pleura is limited by toxicity to the lung and adjacent organs, particularly the bowel and stomach (for left-sided lesions). A retrospective review of 123 patients treated with hemithoracic radiation after surgical debulking of tumour (pleurectomy/decortication) showed actuarial local control at 1 year of 42% and median survival of 13.5 months.⁹⁸ The lung is

sensitive even to small (palliative) doses of radiation and, in the same study, severe pulmonary toxicity was found in 10% with 1.5% treatment-related mortality at 1 month.⁹⁸ Hemithoracic irradiation with the lung in situ is therefore not indicated for mesothelioma.

Palliative radiotherapy

Retrospective and uncontrolled series suggest that radiotherapy can help relieve pain from mesothelioma in around half of patients treated.^{99–100} Although there are no controlled trials evaluating the effect of field size on pain relief, retrospective studies suggest that palliation of pain can be achieved by treating relatively small volumes of symptomatic disease and using short schedules (1–5 fractions) of radiotherapy.¹⁰⁰ Such schedules have been shown to be effective and well tolerated in palliating pain from both thoracic and non-thoracic malignancy. Large-volume radiotherapy has been used, but its effect is usually short-lived and the need to treat bulky disease (necessitating long treatment times) limits its usefulness.¹⁰¹ Patients with symptoms from mediastinal infiltration such as superior vena caval obstruction have a poor response to radiotherapy and generally have a short survival. Other means of palliation are more appropriate.

Radiotherapy as an adjunct to surgery

When extrapleural pneumonectomy is performed, radical radiotherapy is viewed as an integral part of management and can result in local control in 60–90% of patients, albeit with significant (though acceptable) morbidity.^{71–102} Radiotherapy can be delivered with conventional techniques or with the aid of sophisticated planning and treatment hardware and software known as intensity modulated radiotherapy (IMRT).¹⁰³ Preliminary evidence suggests that this technique does result in improved local control over more traditional ways of delivering radiotherapy.¹⁰⁴ However, no improvement in overall survival has yet been observed as most patients develop progressive disease outside the hemithorax.

Prophylactic radiotherapy

There is a risk of seeding of malignant cells in the scar produced by biopsy and/or pleural drainage, resulting in an uncomfortable subcutaneous tumour (although ulceration is rarely a problem). A randomised trial has shown that the risk of this happening can be reduced from 40% to 0% by the administration of three fractions of radiotherapy to scars.⁸¹ Observational studies and first principles suggest that such treatment should be given promptly (ie, as soon as the wound has healed). However, a recent randomised trial showed that the use of a single dose of radiotherapy was ineffective for prophylaxis, with recurrences occurring in 10% of sites not given radiotherapy compared with 7% of sites irradiated.¹⁰⁵ However, this study did show a trend for a lower prevalence of seeding with less invasive procedures. The overall rates of drain site disease were 22% for Abrams' needles, 9% for thoracic drains and 4% for fine needle aspirates. Similarly, a randomised study of 61 patients given three fractions of radiotherapy showed no difference in the prevalence of wound seeding at 1 year with 23% of treated patients and 10% of controls developing scar-related nodules (N Rourke, personal communication).

The current recommendation is that patients of good performance status (and therefore longer survival) who have chest wall wounds should be referred for radiotherapy promptly and treated with a three-fraction schedule. If the patient is of poor performance status and/or has had a minimally invasive procedure, radiotherapy may be unnecessary. Tumour seeding can also occur in the abdominal wall after paracentesis for secondary thoracic malignant mesothelioma or primary peritoneal mesothelioma; however, the potential need for either

repeated drainage of ascites or the use of an implantable device may limit the usefulness of prophylactic radiotherapy to this site.

Key points

- **Palliative radiotherapy provides pain relief in about half of all patients.**
- **Palpable masses respond to radiotherapy in about half of all patients.**
- **Breathlessness and superior vena caval obstruction rarely respond to radiotherapy.**
- **Prophylactic radiotherapy may reduce chest wall implantation following invasive procedures, but may be most applicable for patients with a better prognosis and after more invasive procedures.**

Chemotherapy

In general, palliative chemotherapy should be considered for all patients with performance status 0–2. The objective response rate that should be expected is of the order of 20–40%, and two randomised controlled trials have shown significant differences in survival between regimens, implying that chemotherapy may extend the life expectancy of some patients with mesothelioma. This benefit is not dependent on age, stage or histology.^{106–108} However, there is no randomised trial evidence showing that chemotherapy confers better quality of life and survival than supportive care without chemotherapy. These questions continue to be addressed by the BTS study MSO-1 which compares two alternative chemotherapy regimens (single agent vinorelbine and the combination of mitomycin, vinblastine and cisplatin) with active symptom control alone.¹⁰⁹ This trial closed to recruitment with 409 patients randomised and the results are expected by late 2007.

A number of phase II studies of various chemotherapy regimens have demonstrated both objective response rates comparable to those seen in advanced non-small cell lung cancer and worthwhile palliation of symptoms in half or more of the patients treated (table 4). Symptom relief may occur in patients whose tumours have not shown radiological response as defined by conventional criteria.

There has been considerable interest in a new chemotherapeutic agent for malignant mesothelioma, pemetrexed (Alimta; Eli Lilly). The main evidence supporting its use consists of a randomised study which compared a combination of pemetrexed and cisplatin (PC) with cisplatin (C) alone in patients with mesothelioma. The trial showed that the combination regimen extended median survival by nearly 3 months.¹⁰⁶ On the basis of this study, the US Food and Drug Administration (FDA) approved pemetrexed for the treatment of mesothelioma and it has also been licensed for this indication in Europe, including the UK. Inclusion criteria included Karnofsky performance status (PS) ≥ 70 corresponding to WHO or ECOG PS 0–1. Part way through the trial folic acid and vitamin B12 supplementation was introduced to reduce toxicity resulting in three patient subgroups: never supplemented (NS), partially supplemented (PS) and fully supplemented (FS). The sample size was substantially increased to ensure adequate statistical power of the FS subgroup; 456 patients were randomised but eight who did not receive chemotherapy were excluded from analysis. Patients in the PC arm received a median of six cycles while those in the C arm received a median of four cycles. NS patients received a median of two cycles on each arm. Median survival in the whole group was 12.1 months with PC and 9.3 months with C ($p = 0.02$). Among 331 FS patients, median survival was 13.3 months with PC compared with 10.0 months with C

Table 4 Summary of phase II trials of chemotherapy for mesothelioma

Chemotherapy regimen(s)	Number in study	Tumour response (partial)	Medial survival (months)	Symptom relief (%)	Comments	Reference
Mitomycin, vinblastine, cisplatin (MVP)	39 (extended study 150)	20% (extended study 15%)	6 (extended study 7)	62		110, 111
Vinorelbine	29 (extended study 65)	24% (extended study 21%)	10.6 (extended study 13)	50		112, 113
Gemcitabine and cisplatin	21	47.6%	9.5		Benefit reported in symptoms	114
Other gemcitabine and cisplatin studies		16–33%	9.6–13			115–117
Carboplatin		26%	15			118
Irinotecan, cisplatin, mitomycin		35%			Response in 30% of patients previously receiving chemotherapy	119

($p = 0.05$). The investigators reported a tumour partial response rate of 41.3% in the PC arm, but a review by the FDA confirmed only half of these.¹²⁰ Quality of life data, published in abstract form in 2003, reported a significant improvement in quality of life and symptom relief when compared with cisplatin alone.¹²¹ However, full quality of life data have not been published. The subsequent paper reported that 84 patients from the PC arm and 105 from the C arm received second-line chemotherapy which was associated with significant prolongation of survival after adjustment for baseline prognostic factors and treatment received.¹²² This strengthened the conclusion that first-line pemetrexed prolonged survival since the survival advantage was seen despite the fact that more patients in the C arm had received second-line chemotherapy. The subset analyses performed in this study mean that the results should be interpreted with caution. It is important to note borderline significance in survival advantage in the FS group, as well as the fact that the patients were younger and fitter than most with mesothelioma.

Two phase II studies have suggested that efficacy may be approximately similar when carboplatin (in a dose of area under the curve 5) is used instead of cisplatin in combination with pemetrexed.^{123 124} The substitution of carboplatin for cisplatin is associated with reduced symptomatic toxicity (particularly nausea and vomiting) and increased ease of administration with less need for prolonged hydration with intravenous fluids. This has the potential to improve quality of life.

Support for the efficacy of antifolates is provided by similar results from a smaller study of cisplatin with or without raltitrexed (another antifolate) in 250 patients with mesothelioma.¹²⁵ Median overall and 1 year survival with cisplatin vs raltitrexed was 8.8 (CI 7.8 to 10.8) months vs 11.4 (CI 10.1 to 15) months and 40% vs 46%, respectively ($p = 0.05$). There was no detriment to quality of life from raltitrexed. Unfortunately, the manufacturers do not intend to continue development of raltitrexed for treatment of mesothelioma and may stop production for economic reasons, leaving only pemetrexed in this class in the short to medium term.

The message from the randomised studies of pemetrexed and raltitrexed is that, unless cisplatin alone actually shortens survival—which seems unlikely—these drugs probably do confer a small median survival advantage and, as with any chemotherapy, patients whose tumours respond well to therapy are likely to gain more than average in terms of survival. The effects on quality of life are not yet fully evaluated but appear to be beneficial. Despite the need for caution in interpretation of the data, pemetrexed is an agent with demonstrable clinical efficacy in the treatment of mesothelioma and, as such, it is to be welcomed. It is less toxic than alternatives, particularly when used with carboplatin rather than cisplatin, and easily

administered with a 3-weekly outpatient treatment schedule. Pemetrexed is the only drug licensed for the treatment of mesothelioma on the basis of randomised trial evidence and therefore may be considered the drug of first choice, used in combination with cisplatin or carboplatin. Other cheaper agents with useful activity include vinorelbine, gemcitabine, irinotecan and mitomycin, but none has yet been shown to confer a survival advantage in a randomised trial.

All patients who are fit enough to receive chemotherapy (all PS 0–1 and some PS 2 patients) should therefore be given accurate information and should have the opportunity to discuss chemotherapy with a specialist experienced in its use for mesothelioma. Patients who prefer to receive chemotherapy after a discussion of the merits of this form of treatment should be offered it.

Key points

- **Several chemotherapeutic agents can reduce tumour bulk and help symptoms. The combination of pemetrexed and cisplatin significantly prolongs survival compared with cisplatin alone.**
- **All patients with mesothelioma and performance status 0–2 should have the opportunity to discuss the merits of chemotherapy with either an oncologist or a respiratory specialist experienced in the use of chemotherapy for malignant mesothelioma.**
- **There are no published trials comparing either survival or symptom control in patients treated with chemotherapy or best supportive care. The results of the first such trial (BTS MSO-1) are expected by mid 2007.**
- **Further clinical trials of chemotherapy should be encouraged.**

New approaches to treatment

Some new approaches to drug treatment of mesothelioma that may be important in the future are summarised in table 5.

Attempts have been made to improve the outcome after surgery by use of additional treatment modalities. Cytorductive surgery with intraoperative photodynamic therapy has been studied by several groups with disappointing results.¹³²

Supportive and palliative care

Supportive and palliative care of patients with mesothelioma and their families is very important, given that the disease has a poor and relatively well-defined prognosis and that most patients need symptom palliation from the time of diagnosis onwards. The patient, family and general practitioner may often have difficulty in accepting that palliative care is the only

Table 5 New approaches to treatment for mesothelioma

Agent/approach	Mechanism of action	Trial evidence	Reference
Bevacizumab (Avastin)	Monoclonal antibody vascular endothelial growth factor receptor agonist; angiogenesis inhibitor	Proven efficacy in lung, colon, breast cancer. Multicentre trial underway adding bevacizumab to gemcitabine and cisplatin	126
Ranpirnase (Onconase)	Anti-tumour ribonuclease	Phase III trial of doxorubicin with or without ranpirnase nearly complete. Statins may reverse doxorubicin resistance	127
Bortezomib (Velcade)	Proteasome inhibitor	Proven efficacy in myeloma. Phase II (randomised) trial underway in mesothelioma	128
Arginine depletion	Argininosuccinate synthetase, a rate-limiting enzyme in arginine production is deficient in >50% of mesotheliomas	Phase II clinical trial planned	129
Immunotherapy	Newer targeted biological agents are under development	Interleukin-2 and interferon disappointing	130
Gene therapy	Attractive concept but unlikely to be able to eradicate a solid tumour diagnosed late in natural history	Gene therapy no practical use outside small trials. Role may be as part of multi-modality treatment	131

available treatment for the majority of cases. Anger and frustration are common, and there are particular issues in malignant mesothelioma concerning blame for the disease, obtaining benefits and litigation.

The National Institute for Clinical Health and Excellence⁶² describes supportive care as an umbrella term for services encompassing information giving, self-help and support, user involvement, symptom control, psychological support, social support, spiritual support, rehabilitation, complementary therapies, palliative care, end-of-life and bereavement care. Palliative care is described as the active holistic care of patients with advanced progressive illness. Management of pain and other symptoms and provision of psychological, social and spiritual support is paramount. The goal is achievement of the best quality of life for patients and their families. This document does not present a comprehensive account of supportive and palliative care and symptom relief, and more details can be found in standard references.^{133 134}

Referral of the patient and/or their carers to specialist palliative care services is appropriate for a range of issues. These include unresolved symptoms and complex physical, psychosocial or spiritual needs, and end-of-life and bereavement issues.

Key points

- **Most patients need symptom palliation from the time of diagnosis onwards.**
- **Supportive and palliative care aims to provide relief from pain and other physical symptoms and to respond to emotional, psychological, social and spiritual needs.**

Supportive care and the clinical nurse specialist

Clinical nurse specialists have a central role in providing and coordinating the specialist supportive care needs of patients and carers. This includes liaising with services such as specialist palliative care, dietetics, physiotherapy and the spiritual team where advanced specialist supportive care is needed.

Role of the lung cancer clinical nurse specialist

Patients with malignant mesothelioma and their carers should have access to a lung cancer clinical nurse specialist or, where the local incidence of the disease is high, a mesothelioma clinical nurse specialist. Given the rarity of the disease, the complex support and information needs, it is appropriate for those diagnosed with peritoneal mesothelioma also to have access to the lung cancer clinical nurse specialist.

The role of the clinical nurse specialist includes the following core elements:¹³⁵

- Communication
- Information
- Coordinated care
- Nursing assessment
- Patient advocacy
- Accessibility
- Support

Communication

It is usually the consultant that provides the patient with the diagnosis and an initial outline of management and prognosis, and support from a clinical nurse specialist is crucial at this stage. The clinical nurse specialist should be promptly available for further discussion of these issues with patients and their families and carers, and offer supportive information. Rapid communication with the general practitioner should be ensured and should include details of the known extent of the disease, what was said to the patient and the management plan.

It is not unusual for several members of the lung multi-disciplinary team and the general practitioner to be involved in providing medical care, resulting in complex communication pathways that need to be maintained. The clinical nurse specialist should ensure that the patient and/or carer are aware of the need for a Coroner's post mortem examination and report to the Coroner or Procurator Fiscal and that this is confirmed in writing to the general practitioner.

Information

Patients with malignant mesothelioma and their families should have access to verbal and written information about the disease and its symptoms, end-of-life issues, treatments and the medicolegal implications. Regular contact with the clinical nurse specialist allows a steady flow of information according to the patient's needs.

Lung cancer clinical nurse specialists have expressed concerns about obtaining up to date information and maintaining knowledge and expertise in the field of mesothelioma. Information and support for nurses to allow them to meet the needs of their patients with malignant mesothelioma is available from the organisations listed in Appendix 3 (available online at <http://thorax.bmj.com/supplemental>). The clinical nurse specialist should advise (or clarify) patients and their carers that, following a diagnosis of malignant mesothelioma, entitlement to some benefits and allowances is automatic. Applying for benefits requires attention to detail and can be

time-consuming. Patients and carers should be advised to make photocopies of everything they send to benefits centres for their own reference. The clinical nurse specialist should assist in directing or referring the patient and carer to an organisation that can help with the completion of benefit applications. The lung cancer clinical nurse specialist will advise patients about what help is available locally and Macmillan Cancer Support (on freephone 0800 500 800) can also direct people to local benefits advisory organisations. National organisations offering a telephone benefits advice service, including help with completion of claim forms, are listed in Appendix 3 (available online at <http://thorax.bmj.com/supplemental>).

Coordinated care

The clinical nurse specialist facilitates the pathway of care for the patient and the family throughout the illness, ensuring good liaison between hospital services and primary care and access to specialist palliative care services as required. Patients should be made aware of whom to contact in case of need. The community nursing team (palliative care or district nurse) should be made aware of patients diagnosed with malignant mesothelioma within their area. A team approach should then be adopted to meet the nursing needs of the patient.

Nursing assessment

It is good practice to ensure that there is assessment of the needs of both the patient and the family or carers.¹³⁶ Assessment of patients should include physical symptoms and physical functioning, psychological problems, social care needs and need for spiritual support. Assessment of family members and carers includes their concerns and need for support, including eventually bereavement support. Such assessment may need to be repeated at key times during the illness.

Patient advocacy

The limited treatment options, variation in expert opinion and universally poor outcome means that patient preference is particularly relevant when making treatment decisions about malignant mesothelioma. The relationship between the clinical nurse specialist and patient should help elicit patient and carer hopes and expectations and ensure that treatment plans are mutually agreed upon.

Accessibility

Timely access to the health care team is vital to ensure rapid attention to symptoms. The clinical nurse specialist is often best placed to provide a contact point and should be aware of any other points at which the patient may contact the service.

Support

Patients should be directed to an appropriate cancer support group such as the Lung Cancer Support Group. Where there is a sufficient number of patients with malignant mesothelioma, the development of a local Mesothelioma Support Group is recommended. Patients' carers should be offered information about carer support when required.

Key points

- **The lung cancer clinical nurse specialist acts as the key worker facilitating the pathway of care for the patient and the family throughout the illness.**
- **Clinical nurse specialists are pivotal to meeting patients' specific supportive care needs.**
- **Patients with malignant mesothelioma and their carers should have access to a lung cancer clinical nurse specialist.**

- **The clinical nurse specialist should maintain complex communication pathways.**
- **Providing information to people with cancer and carers should be an ongoing process.**
- **The clinical nurse specialist should provide help and guidance to patients and their carers concerning entitlement to benefits and allowances.**
- **Physical, psychological, social and spiritual assessment may need to be repeated at several key times during the illness.**
- **Patient preference is particularly relevant when making treatment decisions about malignant mesothelioma.**
- **Timely access to the health care team is vital.**

Symptom control

All symptoms need a working diagnosis, as some may be caused by concurrent non-cancer related problems. It is often helpful to record symptom severity on a simple scale to assess progress and response to treatment. Relief of pain, breathlessness and other symptoms can occur with response to chemotherapy.

Pain

The treatment of pain in malignant mesothelioma follows the same principles as for any other cancer but can include more specific techniques where initial methods are inadequate. These may necessitate early referral to a specialist pain service. Specific techniques include:

- Transcutaneous electrical nerve stimulation machines and acupuncture.
- Intercostal, paravertebral or brachial plexus nerve blocks.
- Interpleural,¹³⁶ epidural or intrathecal analgesic infusions.
- Local thoracic spine neurolytic blocks.
- Percutaneous cervical cordotomy¹³⁷ (particularly when the patient is still ambulant).

In pain from chest wall involvement the response to opioids is variable because of added inflammatory and neuropathic components. In this situation, the following adjuvant analgesics should be considered early: non-steroidal anti-inflammatory drugs (with gastric cover); steroids (with gastric cover); noradrenergic antidepressants such as amitriptyline; or anticonvulsants such as gabapentin or carbamazepine.

Pain control will be improved by attention to emotional, psychological, social and spiritual problems. Distraction and relaxation techniques and complementary therapies may also be helpful.

Pain associated with localised tumour invasion of the chest wall may respond to radiotherapy.⁹⁹

Dyspnoea

The common causes of breathlessness in mesothelioma are pleural effusion, lung compression and chest wall stiffness. Weakness and malaise, and anxiety or panic will also contribute. Progressive breathlessness should be treated according to general palliative care guidelines⁶² that include pharmacological approaches such as opioids, benzodiazepines and oxygen, and non-pharmacological methods such as breathing exercises and relaxation combined with re-adaptation.¹³⁸

Cough, anorexia, weight loss, fatigue, excessive sweating and depression all occur in malignant mesothelioma and should be managed according to palliative care guidelines.⁶²

Key points

- **Early involvement of a pain relief specialist is indicated if pain is not controlled after initial measures.**
- **Dyspnoea, cough and other symptoms should be managed according to palliative care guidelines.**

PERITONEAL MESOTHELIOMA

The incidence of peritoneal disease, like pleural mesothelioma, has been steadily increasing over the last 30 years, but the ratio of pleural to peritoneal disease in an asbestos-exposed population remains high (in the order of 12:1) and is slowly increasing. Factors favouring the development of peritoneal disease appear to be longer, heavier exposure to asbestos and, perhaps, to mixed dust. Although the age distribution is similar to pleural disease, there is less male preponderance.

Pathology

The disease may be localised, multinodular or diffuse. Epithelioid subtypes are much more common with only about 15% of tumours being either mixed or sarcomatoid. In two-thirds of patients the disease remains confined to the abdomen. The undersurface of the diaphragm is almost always involved, but tumour rarely penetrates through into the thorax. Spread to the omentum, pelvis and right subhepatic space is common.

Well-differentiated papillary and cystic mesotheliomas seem to be a separate disease, distinct from malignant peritoneal tumours. These conditions are unrelated to asbestos exposure, usually occur in women and have a good prognosis.

Symptoms

These are non-specific and include abdominal pains, constipation, weight loss, abdominal distension, palpable masses and ascites. Small bowel obstruction is usually a feature of the terminal stages.

Imaging

The optimal imaging modality is probably CT scanning. This may show omental and mesenteric thickening (the commonest findings), sheet-like masses, tumour nodules and usually only minimal ascites which may be loculated. The differential diagnosis includes peritoneal secondaries from adenocarcinoma, peritoneal endometriosis and pseudomyxoma peritonei. Retroperitoneal nodal enlargement is more in favour of an adenocarcinoma.

Diagnosis

Cytological examination of the ascitic fluid rarely gives an answer but fine needle aspiration of omental masses has been advocated. If the diagnosis is suspected, this can be confirmed by laparoscopy.

Prognosis and treatment

The prognosis is worse than for pleural mesothelioma. In one study the mean survival time was 7.4 months compared with 11.4 months in a group with pleural mesothelioma.²¹ Like pleural mesotheliomas, the epithelioid subtype seems to be associated with a better prognosis, as is youth and a good performance status. There is limited evidence to support the benefit of chemotherapy, although responses are reported and small case series suggest prolonged survival with regimes based on cisplatin and including mitomycin C, doxorubicin and pemetrexed. The role of radiotherapy is unclear and is associated with considerable morbidity but might be considered prophylactically to laparoscopy port sites. It has been suggested that debulking procedures may improve the response to chemotherapy but there are no controlled trials.

It is important to remember that the management of peritoneal mesothelioma should also include multidisciplinary patient care and consideration of medicolegal aspects.

Key points

- **Peritoneal mesothelioma is related to asbestos exposure but is less common than pleural mesothelioma.**
- **The outlook is poor and no treatment has been shown to alter prognosis.**

BENEFITS AND COMPENSATION FOR MESOTHELIOMA

The respiratory specialist and clinical nurse specialist are often best placed to advise patients and families about opportunities for compensation. The legal test is that the diagnosis and causation should be established on the balance of probability. Hence, pathological diagnosis is not mandatory for compensation issues, although an unequivocal diagnosis will remove subsequent room for debate. Patients who cannot identify occupational exposure to asbestos are not eligible for compensation.

Patients may be entitled to claim compensation in two ways:

- (1) A claim for Industrial Injuries Disablement Benefit from the Department of Social Security (via the Benefits Agency) or through the War Pensions Scheme. Other benefits for incapacity and disability may also be payable.
- (2) A Common Law claim for damages from the firm/firms where exposure to asbestos occurred.

Industrial injuries disablement benefit (IIDB)

Industrial injuries benefit is awarded under the terms of the Social Security Contributions and Benefits Act 1992. This Act specifies that the following criteria must be met to qualify for industrial injuries benefit:

- (1) The person must be suffering from a prescribed disease or personal injury which developed after 4 July 1948.
- (2) (a) The claimant must have been an employee, ie, not self-employed and (b) they should have worked in a scheduled occupation, ie, one where there had been exposure to asbestos.

Mesothelioma is designated a Prescribed Disease (D3) under Schedule 1 of the Social Security (Industrial Injuries) (Prescribed Diseases) Regulations 1985. Under new regulations (The Social Security (Industrial Injuries) (Miscellaneous Amendment) Regulations 1997), the schedule of prescribed occupations was broadened to include any occupation in which there has been "exposure to asbestos, asbestos dust or any admixture of asbestos at a level above that commonly found in the environment at large". Thus, work may not have involved the actual handling of asbestos but may have been carried out in its presence, sometimes known as para-occupational exposure.

Procedure for claiming benefit

A claim for IIDB is made by contacting the local Jobcentre Plus or by ringing the Department of Works and Pensions (DWP) enquiry line (0800 88 22 00) and asking to be sent form B1 100 PN(A). A supply of these forms should be available in chest clinics and the doctor or clinical nurse specialist should provide confirmation of the patient's diagnosis in writing. Occasionally the claimant may need help with completion of the form. Leaflets SD5 ("Ill or Disabled because of Work") and NI12 ("If you have an Industrial Disease") may also be helpful.

In 2005 the Industrial Injuries Advisory Council reviewed the term of prescription for all asbestos-related diseases. They

concluded that those for mesothelioma did not require any modification. However, they noted that the uptake of IIDB was less than the Council would have expected and therefore recommended various measures to raise awareness of the provisions of the scheme, one of which has been liaising with the British Lung Foundation to ensure that clinical nurse specialists are fully aware.

Another concern of the Council was the issue of prompt payments for terminally ill claimants, including all cases of malignant mesothelioma. The “90 day” rule for most benefits has already been waived, and measures have been put in place to reduce any administrative delays to a minimum. Providing the claimant qualifies, he or she should get 100% disability benefit backdated to the date of diagnosis/application. Currently, this is approximately £120 per week.

The Council also recognised that, although such claimants are assessed at 100% disablement, because of their poor life expectancy they receive only a fraction of the total amount payable compared with those suffering from less severe prescribed diseases. The Government has indicated that it intends to put in place a long-term solution to ensure that sufferers of malignant mesothelioma can receive compensation so that they themselves can benefit from it while knowing that their families are secure in the future. The Government is presently going out to consultation, and it is anticipated that they will be making some changes to the way in which mesothelioma sufferers are compensated during 2007.

War pensions scheme

Mesothelioma caused by asbestos exposure during service in the defence forces is compensated under the War Pensions Scheme. A claim should be registered with the War Pensions Agency; details of the local office should be in the telephone book or enquires can be made from the Veterans Agency help line (0800 169 22 77). Those in receipt of IIDB cannot also receive a War Pension, and vice versa.

Additional benefits payable for incapacity and disability

Patients should obtain Benefits Agency leaflet SD1 “Sick or Disabled” (available in tape, Braille and a number of languages). This gives full details of the various additional benefits for which they may be eligible:

- (1) Income replacement:
- (a)

For those with adequate National Insurance contributions: Statutory Sick Pay (SSP) or Occupational Sick Pay from the employer for the first 6 months of illness or Short Term Lower Rate Incapacity Benefit where there is no employer to pay. After 6 months Incapacity Benefit (IB) is then payable.
- (b)

For those with inadequate National Insurance contributions: Income Support (IS) for those whose income and capital is below specified limits and/or Severe Disablement Allowance (SDA) after 28 weeks of incapacity for work.
- (2) Help with excess costs of disability:
- (a)

For those with an assessment for Industrial Injuries Disablement Benefit of 100%, Constant Attendance Allowance (CAA) is available.
- (b)

For those not entitled to CAA, Disability Living Allowance (DLA) is available for those whose disability began before their 65th birthday and Attendance Allowance (AA) is available for those whose disability began on or after their 65th birthday.

The lung cancer clinical nurse specialist has a pivotal role in assisting patients with this process. Further, reassessment of benefit entitlement should be encouraged at regular intervals as further benefits may be applicable as the patient deteriorates or upon death.

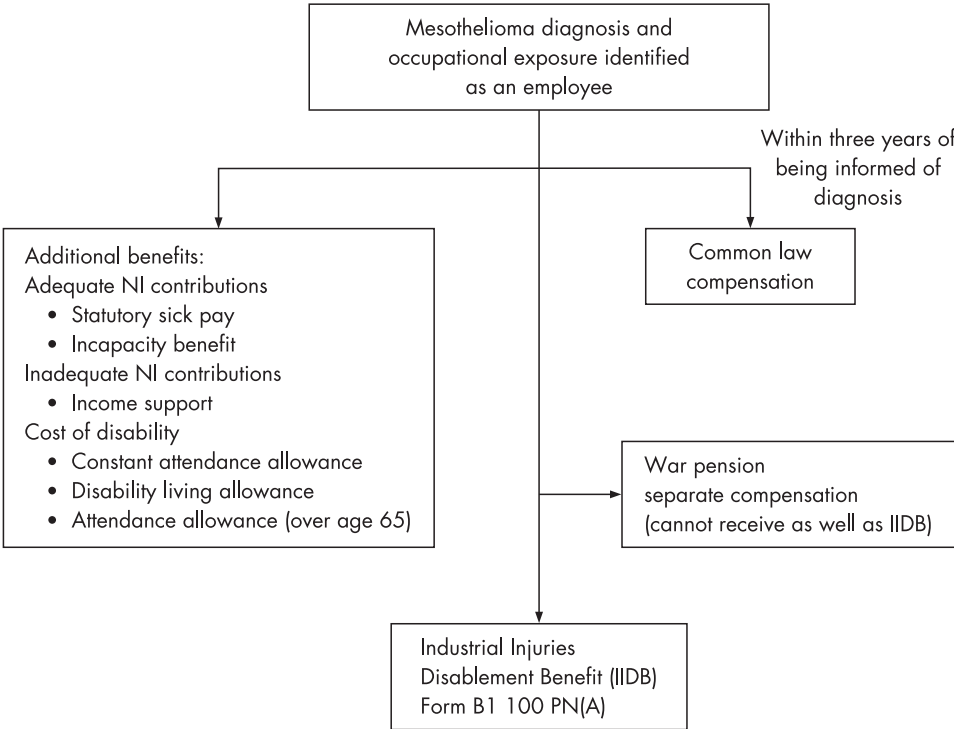


Figure 2 Summary of compensation and benefits for mesothelioma. NI, National Insurance.

Common law compensation

Clinicians seeing any case of asbestos-related lung disease should promptly advise the patient to consider seeking legal advice. This will reduce the risk of subsequent claims for malignant mesothelioma being “statute barred” (see below). Damages may be recovered from an employer by suing them. The claimant must show that, on the balance of probabilities, his or her injuries and/or disability are due to occupational exposure to asbestos, this exposure being attributable to the employer’s negligence in maintaining the standards required by common law. There may also be a breach of the employer’s statutory duty to comply with specific health and safety regulations. Claims can be made against a former employer’s insurer, even if the employer is no longer in business.

Proceedings for these claims must be started within 3 years of the claimant’s “date of knowledge” of any injury caused by asbestos exposure. A claim brought after the expiry of 3 years is generally “statute barred” and it may not be possible to pursue it in the courts. The “date of knowledge” is based on when the claimant first becomes aware:

- (a) that the injury is significant;
- (b) that the injury is attributable in whole or in part to the act/omission alleged to constitute the negligence or breach of duty; and
- (c) of the identity of the defendant.

The date of knowledge is not necessarily the first time a potential claimant is examined by a doctor. The courts have the discretion to extend the 3 year time limit, but the claimant will have to persuade the court to do so.

The Compensation Act 2006 ensures that sufferers can receive full compensation from any of their employers/insurers where asbestos exposure has occurred.

If a patient is awarded damages, the final sum is based on a combination of:

- compensation for pain and suffering (and interest on that);
- loss of earnings (and interest on that);
- care costs;
- other expenses (eg, modifying the home);
- compensation for bereavement.

Compensation under the Pneumoconiosis etc (Workers’ Compensation) Act 1979

For those in whom neither an employer nor an insurer can be identified, a claim can be made to the Department of Works and Pensions under the Pneumoconiosis etc (Workers’ Compensation) Act 1979. The purpose of this scheme is to provide lump sum payments to or in respect of certain persons who are, or were immediately before they died, disabled by pneumoconiosis, byssinosis or diffuse mesothelioma. Eligibility for an award depends on the following criteria being fulfilled:

- (a) Industrial Injuries Disablement Benefit (IIDB) is payable to the claimant in respect of the disease;
- (b) every relevant employer of his has ceased to carry on business; and
- (c) the claimant has not “brought any action, or uncompromised any claim, for damages in respect of the disablement”.

This last criterion means that, if the claimant has already begun a damages claim against the employer and has either settled that claim or that claim ended because the evidence against the employer was weak, then he will not be eligible for

a payment under the scheme of this Act. The lump sum payable is derived from tables which are dependent upon age and the percentage disability of the IIDB, which should be 100% in the case of mesothelioma.

A summary of the compensation and benefits for mesothelioma is shown in fig 2.



Appendices 2 (Staging systems) and 3 (Sources of information and help available for patients and carers, and advice on benefits and compensation) are available online at <http://thorax.bmj.com/supplemental>

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APPENDIX 1: MEMBERSHIP OF THE BTS WORKING PARTY

Professor M G Britton, Consultant Chest Physician, St Peter's Hospital, Chertsey, Surrey; Ms L Darlison, Consultant Nurse, Glenfield Hospital, Leicester; Dr J Entwisle, Consultant Radiologist, Glenfield Hospital, Leicester; Dr M A Greenstone, Consultant Physician, Castle Hill Hospital, Cottingham, Hull; Dr M Hetzel, Consultant Physician, Bristol Royal Infirmary, Bristol; Dr C Higgs, Medical Director, Dorothy House Hospice, Winsley, Bradford-on-Avon, Wiltshire; Dr N Maskell, Consultant Physician, Bristol; Dr M F Muers, Consultant Physician, The General Infirmary, Leeds; Dr R Rudd, Consultant Physician, London Chest Hospital, London; Professor T Treasure, Consultant Thoracic Surgeon, Guys Hospital, London; Dr J Wiggins (Chairman and Editor of Statement), Consultant Physician, Wexham Park Hospital, Wexham, Slough, Berkshire.

Additional contributions were obtained from Dr A Darnton, Epidemiology and Medical Statistics Unit, Health and Safety Executive, Magdalen House, Stanley Precinct, Bootle; Dr M Snee, Consultant Medical Oncologist, Leeds; Dr M Sheaff, Consultant Histopathologist, St Bartholomew's Hospital, London; Ms C Tan, Specialist Registrar, Guys Hospital, London; Dr D R Baldwin on behalf of the BTS Lung Cancer and Mesothelioma Specialist Advisory Group.

EXHIBIT 8

Review

Malignant mesothelioma

Alastair J Moore*, Robert J Parker and John Wiggins

Address: Department of Respiratory Medicine, Wexham Park Hospital, Wexham, Slough, Berkshire, SL2 4HL, UK

Email: Alastair J Moore* - a.moore@ic.ac.uk; Robert J Parker - robertparker@doctors.org.uk; John Wiggins - John.Wiggins@hwph-tr.nhs.uk

* Corresponding author

Published: 19 December 2008

Received: 13 June 2008

Orphanet Journal of Rare Diseases 2008, 3:34 doi:10.1186/1750-1172-3-34

Accepted: 19 December 2008

This article is available from: <http://www.ojrd.com/content/3/1/34>

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Abstract

Malignant mesothelioma is a fatal asbestos-associated malignancy originating from the lining cells (mesothelium) of the pleural and peritoneal cavities, as well as the pericardium and the tunica vaginalis. The exact prevalence is unknown but it is estimated that mesotheliomas represent less than 1% of all cancers. Its incidence is increasing, with an expected peak in the next 10–20 years. Pleural malignant mesothelioma is the most common form of mesothelioma. Typical presenting features are those of chest pain and dyspnoea. Breathlessness due to a pleural effusion without chest pain is reported in about 30% of patients. A chest wall mass, weight loss, sweating, abdominal pain and ascites (due to peritoneal involvement) are less common presentations. Mesothelioma is directly attributable to occupational asbestos exposure with a history of exposure in over 90% of cases. There is also evidence that mesothelioma may result from both para-occupational exposure and non-occupational "environmental" exposure. Idiopathic or spontaneous mesothelioma can also occur in the absence of any exposure to asbestos, with a spontaneous rate in humans of around one per million. A combination of accurate exposure history, along with examination radiology and pathology are essential to make the diagnosis. Distinguishing malignant from benign pleural disease can be challenging. The most helpful CT findings suggesting malignant pleural disease are 1) a circumferential pleural rind, 2) nodular pleural thickening, 3) pleural thickening of > 1 cm and 4) mediastinal pleural involvement. Involvement of a multidisciplinary team is recommended to ensure prompt and appropriate management, using a framework of radiotherapy, chemotherapy, surgery and symptom palliation with end of life care. Compensation issues must also be considered. Life expectancy in malignant mesothelioma is poor, with a median survival of about one year following diagnosis.

Disease name and definition

Malignant mesothelioma is a cancer originating from the lining cells (mesothelium) of the pleural and peritoneal cavities, as well as the pericardium and the tunica vaginalis [1]. Its distribution may be uni- or multifocal or may involve the lining cells in a continuous manner.

Epidemiology and aetiology

Before 1950, malignant mesothelioma was so rare that some pathologists even questioned its existence [2]. However, the increasing use of asbestos after the second world war led to the description of a causal relationship between asbestos exposure and the development of mesothelioma in 1960 [3]. Although its use was widely abandoned in the western world in the 1980s, the long latency period between exposure to asbestos and onset of mesothelioma,

which can range from 15 to 60 years [4,5], meant that the mortality rates from mesothelioma have continued to rise. In the USA the annual deaths from mesothelioma peaked at 3060 in 2002 and have subsequently declined, however the incidence of mesothelioma will continue to rise in the UK until it reaches a peak in about the year 2020 [6]. According to data gathered in the US Surveillance Epidemiology and End Results programme for 1973–1992, there has been virtually a constant rate of mesothelioma in females but a consistently higher rate for males. In the 1960s a mesothelioma register was set up in the UK to systematically record the mortality rates from mesothelioma and to try to identify the incidence of tumour development without known occupational exposure. It is predicted that around 90,000 deaths will occur from mesothelioma by 2050, with 65,000 of these occurring from 2002 onwards [7].

Asbestos is a naturally occurring fibrous silicate, and the risk of developing mesothelioma depends on the exposure to different types of the asbestos mineral fibre. The main asbestos mineral groups are serpentine fibres, which are long and curly, or amphibole fibres which are straight and rod-like. This distinction is important as the serpentine fibre shape is more easily cleared from the respiratory tract. Epidemiologic data suggests that the amphibole, crocidolite, is associated with the highest risk of mesothelioma [8] and that the serpentine fibre, chrysotile has the lowest. The diagnosis of mesothelioma is directly attributable to occupational asbestos exposure; however there is evidence that mesothelioma may result from both para-occupational exposure (e.g.: women having laundered their husband's overalls) and non-occupational "environmental" exposure [9]. **Idiopathic or spontaneous mesothelioma can also occur in the absence of any exposure to asbestos in both animals [10] and humans [8], and a recent review suggests a spontaneous mesothelioma rate in humans of around one per million [11].**

Non-asbestos mineral fibres have also been shown to induce mesothelioma, such as erionite found in certain areas of Turkey [12] or tremolite in north-western Greece [13], and whilst not specifically mined for commercial purposes, tremolite is often found as a contaminant of chrysotile asbestos and has been causally linked with an increased risk of mesothelioma [14]. The role of Simian virus (SV-40) in the pathogenesis of mesothelioma is more controversial; SV-40 was found to contaminate polio vaccines in the 1950s and 60s in the UK, and although it has been suggested that it is a causative factor in the development of mesothelioma [15–17], recent studies have found no link [18–20].

Clinical description

Mesothelioma is primarily a disease of adults and usually presents in the fifth to seventh decades, and 70–80% of cases occur in men. Those diagnosed between the ages of 20 to 40 years usually have a history of childhood exposure [1]. Typical presenting features are those of chest pain, dyspnoea or both [11,21], and in one series up to a third of patients presented with breathlessness due to a pleural effusion without chest pain [22]. When it occurs, the chest pain tends to be dull or boring in nature, but a pleuritic-type pain can occur in the presence of pleural effusions. Involvement of the mediastinal structures is well recognized but hoarseness of the voice and superior vena caval obstruction only rarely causes major symptoms. Dysphagia can also occur but this is a late finding. Unlike bronchogenic carcinomas, presentation with haemoptysis, lymphadenopathy and metastatic symptoms are unusual. A chest wall mass, weight loss and sweating are less common presentations, as is peritoneal mesothelioma although involvement may be found in up to one third of cases at autopsy. Presentation of peritoneal mesothelioma is with non-specific symptoms including loss of appetite, nausea and vomiting, diarrhoea or constipation and occasionally ascites. Small bowel obstruction is usually a late feature, and overall the prognosis of peritoneal mesothelioma is worse than pleural mesothelioma with a mean survival time of about 7 months [11].

Physical examination is usually unremarkable except for signs of pleural effusion and pleural thickening due to tumour infiltration. Finger clubbing is more common than in benign asbestos related pleural disease, and can occur in up to 30% of cases [23]. The tumour originates mainly on the parietal pleura and spreads via the fissures, to encase the lung surfaces. Infiltration of the pericardium can result in signs of cardiac tamponade, and mesothelioma can grow along needle tracks and incisions. Blood tests can reveal an elevated erythrocyte sedimentation rate (ESR) [24], and there have been isolated case reports of mesothelioma associated with autoimmune haemolytic anaemia [25].

Diagnosis and differential diagnosis

The combination of accurate history, examination, radiology and the acquisition of pathology is essential in the diagnosis of mesothelioma. A careful history of asbestos exposure is essential, and the identification of at-risk occupations are strong markers of exposure. However, the delay between exposure and presentation may naturally preclude accurate recall of occupational exposure and working conditions which may have occurred up to 60 years previously.

In those patients with a pleural effusion, sampling of the fluid for cytological examination is the first step in con-

firming the diagnosis. Pleural fluid cytology is positive for malignant cells in about a third of cases [1] and if the clinical, radiological and cytological results support a diagnosis of mesothelioma then this can be accepted. However, it is uncommon for the definitive diagnosis to be made on pleural fluid cytology alone and pleural biopsy for tissue diagnosis is therefore recommended. A contrast enhanced computed tomogram (CT) scan is essential to both identify the extent of the disease, and help guide a percutaneous biopsy if the pleural fluid cytological analysis is not sufficient.

Radiological findings

Radiological imaging is essential for the diagnosis, staging and management of mesothelioma. X-ray, CT, magnetic resonance imaging (MRI) and positron emission tomography (PET) have all been used to evaluate the disease.

CT

Intravenous contrast-enhanced CT is the primary imaging modality for suspected pleural malignant disease. CT allows visualisation of the whole pleural surface and diaphragm and use of a 45–60 second scan delay enables the pleural surfaces to be studied whilst still allowing assessment of the mediastinal nodes [26]. A standard protocol should include the liver and adrenal glands, but in cases where there is a past history of abdominal or pelvic malignancy, the scan should also include the lower abdomen and pelvis [11].

Distinguishing malignant from benign pleural disease can be challenging. The most helpful CT findings suggesting malignant pleural disease are 1) a circumferential pleural rind, 2) nodular pleural thickening, 3) pleural thickening of > 1 cm and 4) mediastinal pleural involvement [27]. The specificities of these findings were 100%, 94%, 94% and 88% respectively. The sensitivities were 41%, 51%, 36% and 56% respectively. The presence of bilateral pleural calcification on CT is uncommon in malignant mesothelioma [27]. A significant reduction in thoracic volume seen on CT is more common, however, occurring in up to 73% of cases according to some series [28]. Whilst these features have a high positive predictive value, absence of these signs does not reliably exclude the diagnosis of pleural malignancy.

MRI

MRI screening is not used routinely in the assessment of malignant mesothelioma, however in patients with potentially resectable disease, MRI can help to provide additional staging information over and above CT. Using gadolinium enhancement, MRI can improve the identification of tumour extension into the diaphragm or chest wall, allowing better assessment of the individual for surgical treatment. MRI also is the imaging modality of

choice in those in whom intravenous iodinated contrast is contraindicated [29].

PET

The standardized uptake value (SUV) in PET is a semi-quantitative measure of the metabolic activity of a lesion and the SUV is significantly higher in mesothelioma than in other benign pleural diseases such as pleural plaques or inflammatory pleuritis [29,30], and one study found PET scanning to have a 96.8% sensitivity and an 88.5% specificity at distinguishing benign from malignant pleural disease [31]. PET scanning has also increased the accuracy in diagnosing mediastinal nodal metastases [30] and therefore the combination of metabolic and anatomical information provided by PET makes it useful in the staging and preoperative evaluation of mesothelioma. PET may also help as a guide to the optimal site for CT guided pleural biopsy, and there is evidence that changes in the fluorodeoxyglucose (FDG) uptake within the tumour might indicate response to treatment suggesting its role in the assessment of response to both chemotherapy and chemo-radiotherapy [32].

Staging and assessment of disease response

At least six different staging systems have been suggested for malignant mesothelioma, but none have been accurately shown to predict survival. Currently, a TNM staging system (Table 1) similar to that used in non-small cell lung carcinoma has been proposed by the International Mesothelioma Interest Group (IMIG) [33].

Tumour response to treatment is an important surrogate for patient benefit. The World Health Organization (WHO) criteria for tumour response were most useful for measuring bi-dimensional lesions, whereas the irregular growth pattern of mesothelioma as a rind around the chest wall makes these criteria poorly applicable [34]. More recently, the Response Evaluation Criteria in Solid Tumours (RECIST) [35] uses a uni-dimensional measurement of tumour size to assess response, but this is based on the assumption that tumours are largely spherical, so again there are limitations to the applicability of this technique in the assessment of malignant mesothelioma.

A modified RECIST criteria has now been published, however, with particular reference to malignant mesothelioma [36]. Assessment of response to treatment is now made by measuring uni-dimensional tumour thickness perpendicular to the chest wall in 2 sites at three different levels on CT.

Pathological findings

According to the WHO classification, malignant mesothelioma can be classified as epithelioid, sarcomatoid, or biphasic based on tissue obtained by biopsy. The patho-

Table 1: IMIG TNM staging system

Primary tumour (T)	
T1a	Tumour limited to the ipsilateral parietal including mediastinal and diaphragmatic pleura, no involvement of the visceral pleura
T1b	Tumour involving the ipsilateral parietal including mediastinal and diaphragmatic pleura, scattered foci of tumour also involving the visceral pleura
T2	Tumour involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with at least one of the following features: • involvement of diaphragmatic muscle • confluent visceral pleural tumour (including the fissures) • extension of tumour from visceral pleura into the underlying pulmonary parenchyma
T3	Locally advanced but potentially resectable tumour; tumour involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with at least one of the following features: • involvement of the endothoracic fascia • extension into the mediastinal fat • solitary, completely resectable focus of tumour extending into the soft tissues of the chest wall • non transmural involvement of the pericardium
T4	Locally advanced technically unresectable tumour; tumour involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral) with at least one of the following features: • diffuse extension or multifocal masses of tumour in the chest wall with or without associated rib destruction • direct transdiaphragmatic extension of tumour to the peritoneum • direct extension of tumour to the contralateral pleura • direct extension of tumour to one or more mediastinal organs • direct extension of tumour into the spine: tumour extending through to the internal surface of the pericardium with or without a pericardial effusion • tumour involving the myocardium
Lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes
N2	Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes including the ipsilateral internal mammary nodes
N3	Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes
Metastases (M)	
Mx	Presence of distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

logical diagnosis is reached with the aid of immunohistochemistry to demonstrate the presence of mesothelial, epithelial, or true sarcomatous differentiation in the malignant cells [37]. The reported diagnostic yield from CT guided biopsy varies from 60% with a single attempt up to 85% with multiple attempts [38]. Ultimately, how-

ever, the highest yields are obtained with open or thoracoscopic pleural biopsy.

There is currently no individual immunohistochemical mesothelial marker that provides 100% specificity and high sensitivity for the diagnosis of malignant mesotheli-

oma [37] and so a number of mesothelial and epithelial markers have been developed. Clearly, distinguishing a malignant pleural process from an inflammatory process is a priority and immunohistochemistry has demonstrated that mesothelioma frequently shows immunoreactivity for keratin, p53 and epithelial membrane antigen (EMA) which is unusual for benign pleural disease.

Differentiating malignant mesothelioma from other malignancies, however, can be more difficult as mesotheliomas, especially those of the epithelioid type, can mimic several other tumours. Again, immunohistochemistry can help in the differentiation of mesothelioma and markers such as mesothelin, cytokeratin 5/6, calretinin, thrombomodulin and WT-1 have been used. The most specific and sensitive markers for mesothelioma are mesothelin (in epithelioid mesothelioma), calretinin and cytokeratin 5/6. However, according to a recent review article, mesothelin is positive in 27% of squamous cell carcinomas, and calretinin and cytokeratin 5/6 can be raised in both squamous cell carcinoma of the lung and adenocarcinoma of both the lung and other sites [37]. Clearly there can be difficulty in making the diagnosis, and so usually a panel of two positive and two negative markers will be sufficient to confirm the presence of malignant mesothelioma.

Serum markers in the diagnosis of mesothelioma

Reliably diagnosing malignant mesothelioma early in the disease is notoriously difficult due to the variability in time to presentation from exposure in the disease. Recently there has been much interest in the use of serum markers for the diagnosis of the disease. The ideal serum marker would be one that is able to offer: 1) early diagnosis, 2) identification of all the subtypes, 3) differentiation of malignant mesothelioma from benign pleural disease and other metastatic pleural malignancies, and 4) be able to track response to therapy and predict survival. As yet no such ideal marker exists, but studies have suggested the use of osteopontin, mesothelin or megakaryocyte potentiating factor in this role.

Osteopontin is a glycoprotein that is over-expressed in lung, breast, colorectal, gastric and ovarian carcinomas and in melanoma. Increased levels correlate with tumour progression, invasion and metastases. Although increased levels do not exclude other malignancies, recent data suggest that osteopontin has great potential use as a marker for mesothelioma [39] and has a positive predictive power for mesothelioma equivalent to Ca-125 for ovarian cancer. Studies have suggested a sensitivity and specificity for mesothelioma of 77% and 85% respectively [40].

Mesothelin is a membrane bound glycoprotein expressed by mesothelial cells and over expressed in malignancy, especially mesothelioma [41]. Soluble mesothelin related

proteins (SMRP) are serum proteins thought to be released by alternative splicing of the mesothelin protein and thereby preventing adherence to cell membranes. Serum concentrations are increased in malignant mesothelioma, and therefore this protein is a potential serum marker for the disease [42]. However, although most patients with mesothelioma have raised serum levels of SMRP, giving a sensitivity of between 80–83% and specificity between 80–100% [43–45], it is mostly associated with the epithelioid sub-type, leading to difficulties in identifying the other sub-types of mesothelioma, especially sarcomatoid, using this marker alone [46]. Nevertheless a commercially available FDA-approved assay, MESOMARK (Fujirebio Diagnostics Inc, Malvern, PA, USA), has been recently approved for use in the monitoring of disease in epithelioid and biphasic mesothelioma, and data seems to support its usefulness [47].

Megakaryocyte Potentiating Factor (MPF) is secreted by cells of several mesothelioma cell lines. In recent studies, MPF was elevated in 91% of 56 malignant mesothelioma patients compared with controls, and levels returned to normal after surgery in patients with peritoneal mesothelioma [46,48]. This might make MPF useful in the monitoring of treatment response in mesothelioma.

Management

Because there can be difficulty reaching a diagnosis of mesothelioma despite radiology, cytology and biopsy, the general management of patients with mesothelioma should be under a multidisciplinary team including respiratory physicians, oncologists, radiologists, palliative care physicians and lung cancer specialist nurses. In addition, once the diagnosis has been reached, there should be close liaison with the patient's primary care physician, and both the primary care physician and family should be warned that, at least in the UK, a post mortem examination will usually be required after the death of a patient with mesothelioma.

The general treatment strategy of mesothelioma should cover the following areas:

- Management of pleural effusions
- Radiotherapy to intervention sites
- Suitability for radical surgery
- Suitability for clinical trial entry and chemotherapy
- Compensation issues
- Palliation of symptoms and end-of-life care

Management of pleural effusions

Management of malignant pleural effusions begins with therapeutic thoracentesis, which assesses the response of dyspnoea to fluid removal. If symptoms do not respond to thoracentesis, alternative causes of dyspnoea should be sought such as pulmonary thromboembolic disease, or lymphangitis carcinomatosa. Early, successful management on pleural effusions with pleurodesis is essential for the palliation of symptoms and the prevention of a trapped lung. However with repeated thoracentesis, the pleural fluid may undergo loculation making it difficult to drain subsequently and also the risk of pleural infection increases. If a conclusive diagnosis has been made, chemical pleurodesis can be performed via a small bore intercostal chest drain (9–14F), which has equivalent success rates to larger bore chest drains with the added benefit of patient comfort [49,50]. The ideal sclerosing agent is sterile talc, with success rates between 70 and 96% [50–52], although care must be taken to ensure the talc particles are of the optimal calibration to prevent the rare risk of adult respiratory distress syndrome (ARDS) [53].

If a firm diagnosis is yet to be made, and the patient is fit enough for surgery, then thoracoscopy is an extremely useful technique in the management of suspected malignant pleural effusions. This procedure allows visualisation of the pleural surface, enables histological sampling for diagnosis and allows complete drainage of the effusion followed by pleurodesis via talc poudrage.

In patients with a trapped lung, or in whom pleurodesis has failed, a pleuro-peritoneal shunt can be considered. Whilst symptoms can improve in over 90% of patients, complications (including shunt occlusion and infection) occur in 15% and therefore their use is diminishing [54]. More recently, an ambulatory pleural drainage system (Pleur_x Pleural Catheter, Denver Biomedical Inc, USA) has been developed. This system enables the patient to control the pleural effusion at home by means of a long-term drainage catheter and vacuum bottles. This might help patients with trapped lungs as it both avoids the need for surgical intervention, and palliates dyspnoea [55].

Radiotherapy*Palliative radiotherapy*

Radiotherapy can be used to control local tumour growth and occasionally causes regression of disease, but there is no evidence that radiotherapy alone affects survival [56]. It has, however, been shown to be helpful in the palliation of pain [57], and approximately half the patients treated with palliative radiotherapy derive some benefit [58]. It also appears that short courses of radiotherapy (for example 20 Gy in 5 fractions) are as effective as longer courses such as 30 Gy in 10+ fractions [59], although there is a

total dose response effect [60]. Unfortunately, radiotherapy is rarely helpful in either the palliation of dyspnoea or the management of symptoms of mediastinal infiltration such as superior vena caval obstruction (SVCO), and alternative methods of treatment such as SVC stenting should be sought [11,61].

Radical radiotherapy as a single modality

Whilst hemithorax irradiation may provide symptomatic benefit, no studies have shown that it prolongs survival [61]. Mesothelioma can involve large areas of the pleural cavity and use of radical radiotherapy over large fields places a range of organs such as lungs, liver, spinal cord or heart at a significant risk of dose related damage. As a result, a recent Cochrane review found no randomised clinical trial evidence to support the use of radical radiotherapy alone (or in combination with other treatment modalities) in mesothelioma [62], and this treatment option has been shown to confer a significant mortality, with rates as high as 17% in one series [59].

Radiotherapy as part of multimodality treatment

Failure to increase survival using single treatment modalities has led to a multimodality approach to treatment in mesothelioma. Combining debulking surgery with radiotherapy is the cornerstone of this approach and can both reduce systemic recurrence and influence the natural history of the disease [63,64]. Typically, hemithorax radiotherapy is combined with extra pleural pneumonectomy (EPP – see later) and correctly staged patients with epithelioid mesothelioma can have median survival rates of 33 months [65]. Due to the large, irregular nature of malignant mesothelioma along with the close proximity of other organs, a more directed modality of irradiation which could help improve local tumour control whilst limiting exposure to surrounding organs has been developed, known as intensity modulated radiotherapy (IMRT) [66]. Despite the possibilities for improved tumour control, however, IMRT still carries a potential risk of fatal pulmonary toxicity in mesothelioma [67,68].

Prophylactic radiotherapy

Mesothelioma may seed malignant cells in procedure scars. Whilst pain from these metastases is rare, they can become uncomfortable, and evidence has suggested that radiotherapy to intervention sites can prevent this complication [69,70]. Whilst this practice is recommended in current guidelines [11], evidence is emerging that it should only be offered to those patients who are symptomatic from these subcutaneous tumours as the radiotherapy itself may have side effects [71,72].

Surgery

The role of surgery in the treatment of malignant mesothelioma is still uncertain. The three most common sur-

gical procedures are surgical pleurodesis via video assisted thoroscopic surgery (VATS), debulking surgery (also known as cytoreductive surgery or pleurectomy/decortication (P/D)) and extra pleural pneumonectomy (EPP). This comprises en-bloc resection of the parietal pleura, lung, pericardium and diaphragm and mediastinal nodes [56]. P/D allows the removal of the visceral, parietal and pericardial pleura as well as debulking the tumour and is therefore less demanding, with mortality rates < 5% [73]. P/D has limitations, however, as it does not remove the tumour completely, and the preservation of the ipsilateral lung makes postoperative radiotherapy difficult due to the risk of pulmonary side effects [74]. The impact of P/D on overall survival is contentious, with some evidence suggesting that P/D surgery via a VATS approach may provide a survival benefit in patients with advanced disease not suitable for EPP [75], whilst other studies do not clearly distinguish the benefit of P/D over EPP [76].

EPP is a much more demanding procedure with morbidity rates as high as 60% [77] and mortality rates of 4–9% [11,78,79]. However, the pneumonectomy in EPP allows the use of high dose hemithoracic radiotherapy, and this combined treatment has been shown to reduce local recurrence and prolong survival in early disease [65]. As a result, as part of the trimodality approach to treatment with surgery chemotherapy and radiotherapy, EPP has arisen as the surgical treatment of choice, albeit without clear randomised controlled trial evidence [78]. In order to clarify this issue, a large randomized trial (Mesothelioma And Radical Surgery (MARS)) is underway [80]. In this trial, EPP is sandwiched between induction chemotherapy and radical radiotherapy. The control arm offers full active tri-modality therapy, although the surgery is limited to debulking surgery. In addition patients receive the same induction chemotherapy and are given radiotherapy to any drain or port sites.

Chemotherapy

The use of chemotherapy in malignant mesothelioma aims to lengthen survival, improve quality of life and provide symptomatic relief. Currently, there is no single drug or combination therapy that could be considered as standard treatment for mesothelioma. A variety of single agent and combination regimens have been tried in clinical trials with response rates of between 0% and 45% [81].

A review of studies by Berghmans *et al* [82] revealed that cisplatin was the most effective single agent for mesothelioma, with carboplatin having similar activity, and in combination with doxorubicin provided a response rate superior to other regimens studied, although there was no clear benefit in terms of survival. Single agent vinorelbine and combination treatment MVP (mitomycin C, vinblas-

tine and cisplatin) have also been shown to provide good symptom relief with acceptable toxicity [83–85].

Recently, there has been much interest in the use of the antifolate pemetrexed (Alimta; Eli Lilly). Pemetrexed exerts its effect by interrupting folate dependent metabolic synthesis of purines and pyrimidines (the building blocks of DNA and RNA), and a Cochrane review of the effectiveness of combination treatment with cisplatin/pemetrexed [81] suggests a survival benefit, albeit with increased toxicity which is reduced by the co-administration of vitamin B12 and folate supplements. Much of the evidence supporting the use of pemetrexed comes from a single study [86] in which 331 patients, fully supplemented with vitamin B12, demonstrated a median survival of 13.3 months with combination pemetrexed/cisplatin compared to 10.0 months with cisplatin alone ($p = 0.05$). This was associated with a significant improvement in quality of life and symptom relief compared to cisplatin alone [87]. Combination with carboplatin instead of cisplatin, however, may be an alternative regimen which provides similar efficacies and reduced side effects [88]. An alternative antifolate agent, raltitrexed, has also been shown to confer a survival benefit in combination with cisplatin, with median overall survival increasing from 8.8 months (CI 7.8–10.8) with cisplatin alone to 11.4 months (CI 10.1 to 15) with combination cisplatin-raltitrexed ($p = 0.05$) [89]. Although this study only demonstrated borderline significance, likely as a result of sample size, the results of these trials mean that combination cisplatin and an antifolate should be the reference regimen in mesothelioma. Recent advances now favour the use of neoadjuvant chemotherapy followed by EPP and radiation for malignant mesothelioma; Weder *et al* recently published their experience of a prospective trial of neoadjuvant chemotherapy consisting of cisplatin and gemcitabine followed by EPP, demonstrating a median survival of 23 months [90]. Similarly, Flores *et al* prospectively studied patients given induction gemcitabine and cisplatin followed by EPP. Median survival of all patients in the study was 19 months, but those patients who completed induction chemotherapy and subsequently underwent EPP had a median survival of 33.5 months [91].

As a result, all patients who are fit enough (ECOG performance status 0–2) should have the opportunity to discuss the merits of chemotherapy in mesothelioma with an oncologist [11], in the knowledge that there are no published data which compares survival or symptom control in patients treated with chemotherapy or best supportive care only. The first such trial (MSO-1) [92] is complete, and the preliminary results were published in abstract form in 2007 [93]. These results suggest that the addition of chemotherapy to active symptom control with best supportive care did not infer a significant survival benefit

in mesothelioma, however this trial was started before the emergence of pemetrexed.

Supportive and palliative care

Given that malignant mesothelioma has a poor overall prognosis, referral of patients to specialist palliative care services will be appropriate at some time in the disease course. Most patients need palliation of symptoms early on in the course of the disease and recognition of this by the patient, family and primary care physician is essential in the management of the patient with mesothelioma. The use of a central lung cancer nurse specialist provides a means by which the patient can gain access to the delivery of care needed for this disease, through the following core elements [11]:

- Communication
- Information
- Coordinated care between respiratory physicians, oncologists, radiologist and palliative care specialists
- Nursing care
- Accessibility
- Support

Prognosis and survival

Life expectancy in malignant mesothelioma is poor, with median survival varying between 8 and 14 months [11]. The Cancer and Leukaemia Group B, and the European Organization for Research and Treatment of Cancer have analysed large numbers of patients enrolled in treatment trials for mesothelioma and have identified the following poor prognostic factors:

- Non-epithelioid histology
- Poor performance status
- Chest pain
- Age older than 75
- Male gender
- White blood cell count $8.3 \times 10^9/L$ or greater
- Platelets greater than 400,000 μL
- LDH greater than 500 IU/L

The majority of patients who survive for more than 2 years have epithelioid histology and death from mesothelioma tends to be due to respiratory failure.

Compensation issues

Eligibility for compensation for mesothelioma may vary from country to country. In the UK for example, a diagnosis of mesothelioma allows compensation via the Industrial Injuries Disablement Benefit, War Pensions Scheme or through a Common Law claim from the firm/firms where the asbestos exposure occurred. Patients who cannot identify occupational exposure to asbestos are not entitled for compensation, however pathological confirmation of the diagnosis is not mandatory; establishing the diagnosis and causation on the balance of probability is sufficient, although an unequivocal diagnosis obviously removes any cause for debate. Earlier this year, a new legislation was made in the UK Child Maintenance and Other Payments Act whereby dependants of persons with mesothelioma became eligible to claim for lump-sum compensation after death <http://www.opsi.gov.uk/acts/acts2008a>.

Abbreviations

ESR: erythrocyte sedimentation rate; CT: computed tomogram; MRI: magnetic resonance imaging; PET: positron emission tomography; SUV: standardized uptake value; FDG: fluorodeoxyglucose; IMIG: International Mesothelioma Interest Group; WHO: World Health Organization; RECIST: Response Evaluation Criteria in Solid Tumours; EMA: epithelial membrane antigen; SMRP: Soluble mesothelin related proteins; ARDS: adult respiratory distress syndrome; MPF: Megakaryocyte Potentiating Factor; SVC/O: superior vena caval obstruction; IMRT: intensity modulated radiotherapy; VATS: video assisted thoracoscopic surgery; P/D: pleurectomy/decortication; EPP: extra pleural pneumonectomy; MARS: Mesothelioma And Radical Surgery.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed to this review article.

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EXHIBIT 9

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Third Edition

Travis et al.¹²⁹ also conclude that treatment (as opposed to genetic susceptibility to tumors) probably explains much of the observed excess tumors in testicular cancer patients, an interpretation supported by the lower risks in the first 10 years of follow-up.

Accordingly, it is our view that ionizing radiation may play a causal-contributory role in the genesis of some mesotheliomas, probably as a cofactor along with innate susceptibility to cancer development (as demonstrated by one or more antecedent cancers), with or without past asbestos exposure, but the number of such radiation-related cases is small in comparison to the burden of asbestos-related MMs, for which radiation is not a co-factor.

Malignant Mesotheliomas in Children (and the Concept of Spontaneous Mesotheliomas)

In 1985 Talerman et al.¹⁵² reported a case of a diffuse malignant deciduoid peritoneal mesothelioma in a 13-year-old girl and reviewed the literature identifying 41 previously reported cases of mesothelioma in children. Thirty-three of the 41 previously reported cases began in the pleura, and 40 of the 41 children died 2 weeks to 21 months after diagnosis, a clinical course similar to that in adults. In many reported cases of mesothelioma in children, a history of exposure to asbestos was not documented, and in Talerman et al.'s case and in two other cases reviewed, there was no history of exposure to asbestos.

Fraire et al.¹⁵³ independently reviewed slides available of 17 children previously diagnosed as having mesothelioma. Upon review, only three cases were confirmed as mesothelioma. Therefore, they concluded mesothelioma in children might be rarer than suspected. Fraire et al.¹⁵⁴ conducted an extended evaluation of 80 reported cases of mesothelioma in childhood. Of the 80 cases, tissue slides were available for review in 22 cases, of which 10 were considered MM, nine nonmesothelial malignant tumors, and three malignant neoplasms of uncertain type. The authors found no relationship between childhood MM and asbestos, radiation, or isoniazid therapy. Lin-Chu et al.¹⁵⁵ reported a confirmed case of MM in a 19-month-old girl. In their review of the literature, they found three other cases of MM in infants. In their case, there was no information concerning exposure to asbestos.

The occurrence of mesothelioma during infancy, childhood, and adolescence supports the notion of true spontaneous mesotheliomas. Diagnosis of mesothelioma during infancy and childhood poses greater difficulties than for adults, especially the distinction from pleuropulmonary blastomas of childhood¹⁵⁶ and perhaps desmoplastic small round cell tumors of the pleura,³⁷ but there is little doubt that childhood mesotheliomas do

occur. From a review of three studies, McDonald and McDonald¹⁵⁷ suggest that the incidence of childhood mesothelioma may be within the range of 0.5 to 1.0 case/10⁷/yr.

Background Exposure to Asbestos and Background or Spontaneous Mesotheliomas: Do They Exist? It is our perception that background asbestos exposure from the environment at large represents general environmental exposure unrelated to the use of asbestos-containing materials in the workplace or at home, or from significant point sources of asbestos such as factories. We consider background exposure to include exposures related to the passive weathering of in-place asbestos-containing materials, including asbestos-cement roofing materials with very low or unmeasurably low airborne fiber concentrations, and environmental exposure derived from the brakes of passing automobiles; we exclude from "background" any exposure arising from active disturbance of any asbestos-containing materials such as asbestos-cement building products or insulation materials.

It is also important to recognize that absence of a history of asbestos exposure does not equate to absence of exposure. Many cases of seemingly background MM can be attributed to long-past forgotten or unrecognized asbestos exposures. For example, many of the cases that are encountered in our everyday or referral practice are accompanied by a clinical statement that no asbestos exposure has been identified, but subsequent and more detailed history-taking usually does yield a history of brief exposure to asbestos, and in some of those cases the mesothelioma patient was unaware that the material used (e.g., fibrous cement building materials) did in fact contain asbestos. The problem of detailed and systematic history-taking is also exemplified by some of the data in the Australian Mesothelioma Surveillance Program, in which a substantial number of the cases initially classified as having no known exposure history in fact had asbestos exposure documented upon more detailed review.⁴³

The often-cited background MM rate of 1 to 2 per million person-years, was derived partly from backward extrapolation of the incidence rates in men, to the point where the rates for men and women diverged from each other, based on a presupposition that the female incidence rate for mesothelioma has been stable, and that most MMs in women represent background cases.¹⁵⁸ In reality, there is persuasive evidence that both of these assumptions are false: (1) in the United Kingdom the death rate for MM in females increased from 4.67/10⁶/yr in 1989–1991 to 5.77 in 1995–1997,¹⁵⁹ and to 9.75 in 2002–2004; (2) the female incidence rate in Australia rose about threefold over a period of ~20 years; (3) Strickler et al.¹⁶⁰

also recorded a rising incidence of MM in the U.S. for women aged 45 to 54 years and above, for the period 1975–1997, based on SEER data, which cover about 14% of the U.S. population; and (4) among female MM patients, up to ~75% in some series^{36,161} had a history of asbestos exposure, but the exposures were occupational in only a minority (~20%),¹⁶¹ so that nonoccupational exposures such as domestic (household contact) exposure constitute a much higher proportion of MM cases among women than in men.¹⁶¹ As foreshadowed in the preceding discussion, Roggli et al.¹⁶¹ found that the lung tissue asbestos burden was elevated in 70% of a series of female MM patients in the U.S., and the main fiber type detected was amosite, followed by tremolite and chrysotile, and the lung tissue asbestos body and fiber concentrations as a consequence of such domestic exposure approached those found with some patterns of occupational exposure.¹⁶²

The background environmental mesothelioma incidence rate and especially the true spontaneous rate is probably substantially less than one case/10⁶/yr, but the true rate can only be guessed, because no significant control adult population without asbestos fibers in lung tissue can be assembled.¹⁶³

Hereditary Factors and the Role of Genetic Susceptibility

Mesothelioma occurs in only a minority of asbestos-exposed individuals, even in those exposed heavily to amphibole asbestos.³⁶ This observation might be explicable by mesothelioma induction as a chance event; that is, mesothelioma is the outcome of a multistage process involving multiple mutational and epigenetic events, so that most of those exposed to asbestos simply do not strike the correct combination of a complex set of events necessary for development of mesothelioma. Alternatively, one of the mutations induced by asbestos may be lethal to the initiated cell, so that subsequent steps cannot occur (see Molecular Pathogenesis and Pathology of Malignant Mesothelioma, below). However, alternative explanations include (1) modulation of the asbestos-imposed risk by genetic or acquired susceptibility/resistance factors,¹⁶⁴ or (2) a combination of randomness and predisposition.

In 1985 Lynch et al.¹⁶⁵ described the occurrence of epithelial mesotheliomas in two brothers who had been exposed to asbestos, and reviewed the literature citing three other reports of familial mesothelioma. Ten of 11 family members in the four families reported had a definite history of exposure to asbestos. In 1984 Martensson et al.¹⁶⁶ reported two pairs of siblings, a brother and sister and identical twin brothers, who developed pleural MMs. Both pairs of siblings had exposure to asbestos. We reported three brothers who had an asbestos insulation

business; two developed mesotheliomas that arose in the pleura and the other brother had peritoneal mesothelioma.¹⁶⁷ Subsequently, one male child and one female child in this family died from pleural MM.

Other studies have evaluated hereditary factors in mesothelioma. Huncharek et al.¹⁶⁸ studied 39 cases of pleural mesothelioma and 259 age-matched controls to assess the possibility of influence of family history on pleural MM risk. Twenty-eight (71%) cases reported a parental history of cancer versus 114 (44%) in the control group ($p < .01$), suggesting a possible role for a family history of cancer in the development of pleural mesothelioma.

Heineman et al.¹⁶⁹ evaluated mesothelioma, asbestos, and reported history of cancer in first-degree relatives. Specifically, they compared reported histories of cancer in first-degree relatives of 196 patients who had a pathologic diagnosis of mesothelioma, with those from 511 deceased controls. The authors found only limited suggestive evidence that a family history of cancer may be a risk factor for mesothelioma, possibly in conjunction with asbestos exposure. Studies of small family clusters, including that of Ascoli et al.¹⁷⁰ in relatives working in a confectionary shop highlighted the possibility that inherited factors might be involved in the development of MM. We have seen a number of other familial cases of mesothelioma where two or more family members developed mesothelioma, usually in a setting of occupational or domestic bystander asbestos exposure (Fig. 43.4).

A larger survey conducted by Bianchi et al.¹⁷¹ included 610 pleural mesotheliomas of which 40 were found to be familial. Familial mesotheliomas included 31 men and nine women with an age range of 44 to 93 with a mean of 70.7 and a median of 71.0 years. In 15 families, there were blood relations between or among the members involved. However, all patients had reported exposures to asbestos, mostly in the shipyard.

Ohar et al.¹⁷² tried to identify a more extensive set of traits that would define a mesothelioma phenotype for the purpose of genetic analysis. They found that compared to other asbestos-exposed groups, subjects with mesothelioma were younger at first asbestos exposure, had a greater risk of second cancer diagnosis, had a longer disease latency, and had a greater risk of cancer among first-degree relatives. The authors concluded that thoracic tumor location, work exposure, male gender, long latency, early age at first exposure, presence of a second cancer, and first-degree relative with cancer defined a phenotype that distinguishes mesothelioma patients with a short survival from other asbestos-exposed individuals. They proposed this phenotype could be applied to candidate gene analysis.

Several studies have attempted to determine a cytogenetic profile for MM. Ascoli et al.¹⁷³ performed genomic

EXHIBIT 10

US mesothelioma patterns 1973–2002: indicators of change and insights into background rates

Mary Jane Teta^a, Pamela J. Mink^{b,d}, Edmund Lau^c, Bonnielin K. Scurman^b and Edward D. Foster^b

Mesothelioma rates are declining toward background levels, although estimates of the background rate have varied. We expanded upon earlier analyses and provided a data-based estimate of the background rate. We analyzed US male and female patterns for five age groups using the National Cancer Institute's Surveillance Epidemiology and End Results registry data from 1973 to 2002. Age-specific and age-adjusted incidence rates per 1 000 000 persons per year, standardized to the 2000 US population, were calculated for total, pleural, and peritoneal mesothelioma. We also calculated rates for persons who attained working age after the US Occupational Safety and Health Administration asbestos exposure limits took effect. Mesothelioma rates observed among young males and females varied little over time. We observed a decline and convergence of recent male and female rates in older age groups, except those who are between the age of 60 and above, for whom the 2002 male rate was approximately five times greater than that of females. As expected, rates were higher in major shipyard areas on the West coast. Rates for persons with little or no opportunity for occupational asbestos exposure were 1.15 (95% confidence interval: 0.90–1.45) for men and 0.94 (95% confidence interval: 0.87–1.24) for women. Mesothelioma is rare in younger age groups, and rates have been relatively stable and similar

for both sexes. Rates continue to decline in older age groups, but remain high for males at 60 years or older. Rates among females at older ages suggest an impact of occupational exposure. **The background rate for persons below age 50 is approximately one per million, independent of sex.** Future data are needed to estimate this rate for older age groups. *European Journal of Cancer Prevention* 17:525–534 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

European Journal of Cancer Prevention 2008, 17:525–534

Keywords: asbestos, epidemiology, incidence, mesothelioma, National Cancer Institute's Surveillance Epidemiology and End Results program, trends

^aExponent Inc., Health Sciences Practice, New York, New York, ^bExponent Inc., Health Sciences Practice, Washington, District of Columbia, ^cExponent Inc., Health Sciences Practice, Menlo Park, California and ^dDepartment of Epidemiology, Rollins School of Public Health, Emory University, Georgia, USA

Correspondence to M. Jane Teta, Dr PH, Exponent Inc., Health Sciences Practice, 8 Dogwood Court, Middlebury, CT 06762, USA
Tel: +1 203527 4049; fax: +1 203527 4049;
e-mail: jteta@exponent.com

Received 8 March 2007 Accepted 4 August 2007

Introduction

Diffuse malignant mesothelioma is a rare and rapidly fatal tumor, and exposure to asbestos is considered as the primary etiologic agent (Light, 2005). Results from epidemiologic studies have supported the theory that the increased incidence of mesothelioma observed in the 1970s and 1980s worldwide is related to the increased occupational asbestos exposures from the 1930s through the 1960s (Nicholson, 1982; Price, 1997; Leigh *et al.*, 2002; Neuberger and Vutuc, 2003; McElvenny *et al.*, 2005). The latent period between the time of first exposure and clinical manifestation of disease is thought to be between 20 and 40 years, although even longer latencies have been observed internationally as cases continue to arise as a result of shipyard and military service exposures during and after World War II (Xu *et al.*, 1985; Lanphear and Buncher, 1992; Bianchi *et al.*, 1997; Polednak, 2003; Ulvestad *et al.*, 2003).

Mesothelioma incidence rates vary according to age, sex, time period, and geography. Different temporal patterns

among these groups reflect the impact of historical, occupational, and in some regions, environmental asbestos exposures.

European epidemiologic studies have reported male age-adjusted death rates ranging from 7 per million in Hungary to 24 per million in the Netherlands from 1990 to 1994 (Peto *et al.*, 1999; La Vecchia *et al.*, 2000). Australia, with its long history of asbestos mining and ubiquitous uses, had an annual incidence rate of 59.8 per million for men and 10.9 per million for women in 1997 (Leigh *et al.*, 2002). Surveillance of mesothelioma in Africa has been limited, but reported incidence rates have been comparatively low (Parkin *et al.*, 2002). Incidence rates in Asian countries are also low as compared with Europe, Australia, and North America (Parkin *et al.*, 2002; Kanazawa *et al.*, 2006; Murayama *et al.*, 2006).

In the United States, the average annual age-adjusted incidence rates of mesothelioma for the years 1998–2002 are estimated to be 20 per million for males and 4 per

million for females. The rates for males in older age groups, however, are much higher than the overall average, and higher than females in this age group (Ries *et al.*, 1975). Studies have reported an increased risk of mesothelioma in areas with occupational asbestos exposure from shipbuilding, such as California and Seattle, from 1934 through about 1975, when the Navy ceased using amphiboles for insulation in vessels (Fleischer *et al.*, 1946; Fisher, 1998, 2001; Rushworth, 2005).

Although the majority of mesothelioma cases have shown a definite history of earlier exposure to asbestos, scientific evidence suggests that a proportion of cases occurred with no apparent history of asbestos exposure (McDonald and McDonald, 1980; Spirtas *et al.*, 1994). It is generally well-accepted, therefore, that there is a background rate of mesothelioma, unrelated to asbestos exposure (Walker *et al.*, 1983; McDonald, 1985; Ilgren and Wagner, 1991; McDonald and McDonald, 1994; Huncharek, 2002; Price and Ware, 2004).

Some studies have attempted to estimate the background incidence rate of mesothelioma. As occupational exposure to asbestos among women is relatively uncommon, the female incidence rate of mesothelioma has been considered by some authors to be a reasonable estimate of background incidence (Ilgren and Wagner, 1991; Price and Ware, 2004). McDonald (1985) estimated the background level of mesothelioma to be 1–2 per million in both men and women, using the historical rate in the 1950s when male and female rates diverged. Price and Ware (2004) hypothesized that if all female cases were not exposed to asbestos, the background rate would be 4 per million. Hillerdal (1999) suggested that the 'natural level' is much lower than 1 per million but acknowledged the uncertainty in this estimate.

Since the establishment of asbestos exposure limits by the U.S. Occupational Safety and Health Administration in 1972 (36 Federal Register 23207), occupational exposure to asbestos has declined considerably. Given the reduction in overall exposure to asbestos over the past three decades, incidence rates should be showing signs of declining toward background levels. Price and Ware (2004), using data from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program, concluded that mesothelioma incidence rates have remained relatively stable since 1992, and that after a predicted peak of cases in 2000–2004 a return to background levels would occur by 2055. In a similar analysis, Weill *et al.* (2004) observed a decline in male incidence rates in the early 1990s after two decades of increasing rates, suggesting further declines of mesothelioma in the future. The analyses of both reports were based on age-adjusted incidence rates from the SEER program through the year 2000.

We expanded upon earlier analyses by using SEER data through the year 2002, evaluating rates by sex, age group, year of diagnosis, and primary site to elucidate more clearly changes owing to reductions in occupational asbestos exposure, and to estimate rates of mesothelioma among men and women unlikely to have opportunities for asbestos exposure. To illustrate the influence of geographic region, we also used SEER data to examine rates in the three California SEER registries, comparing them with each other and to the other SEER registries.

Materials and methods

Data source

We used mesothelioma incidence data for cases reported during 1973–2002, collected by nine SEER program cancer registries. Data from the regional registries in Los Angeles County and San Jose/Monterey are available for the years 1992–2002. Data from the nine SEER registries represent approximately 10% of the total US population. With the addition of the two regional registries in California, the SEER registries cover approximately 14% of the US population (Hankey *et al.*, 1999). With the addition of Alaska and rural Georgia, also available since 1992, data from up to 13 registries can be selected for analyses for the years 1992–2002. We used the SEER 9 Registries Database (2005a) and the SEER 13 Registries Database (2005b), both of which are available to the public.

Data analysis

Unless noted otherwise, data were analyzed using SEER*Stat software [Surveillance Research Program, National Cancer Institute SEER*Stat software (www.seer.cancer.gov/seerstat) version 6.1.4]. We created five groups to represent age at diagnosis as follows: less than 20, 20–39, 40–49, 50–59, and ≥ 60 years. Age-specific and age-adjusted (five groups) incidence rates per 1 000 000 persons per year, standardized (direct method) to the 2000 US population, were calculated for total mesothelioma, pleural mesothelioma, and peritoneal mesothelioma. Data were analyzed separately for males and females. Comparisons of rates from the three regional SEER registries in California combined were limited to the years 1992–2002.

To evaluate mesothelioma rates among men and women with little or no potential for occupational asbestos exposure, we limited the analysis to those diagnosed at the age of 30 years or above, and who attained working age after the OSHA asbestos exposure limits took effect.

For these analyses, mesothelioma cases were restricted to persons born between 1953 and 1972 (inclusive), and diagnosed between 1983 and 2002 who, therefore, were between the ages of 30–49 years at diagnosis. The nine SEER cancer registries with data from 1973 to 2002 and

the additional four registries with data from 1992 to 2002 formed the basis for this analysis.

Cancer rates were indexed by sex, year of birth, year of diagnosis, and 95% confidence intervals (CI) were constructed by using the Poisson approximation formula proposed by Rothman and Boice (1979). CIs for rate ratios were calculated on the basis of standard approximation formulas (Rosner, 2003).

Results

Mesothelioma patterns by age, sex, and time period

Mesothelioma occurs rarely in children (ages 0–19 years), for whom the annual rate is well under 1 per million. Of the 6078 cases reported in the nine SEER registries during 1973–2002, only eight cases were younger than 20 years of age at diagnosis (Table 1). For adult males, mesothelioma incidence rates increased with age during this same time period: 0.7 (20–39 years), 5.1 (40–49 years), 19.1 (50–59 years), and 92.3 (60+ years). Female adult rates also increased with age, but less dramatically: 0.6 (20–39 years), 2.5 (40–49 years), 6.0 (50–59 years), and 15.5 (60+ years). At ages younger than 40 years the male and female rates were similar, but clearly diverged at older ages with male rates being about three times greater than female rates at age 50–59 years, and six times greater at age 60 years and above.

In addition, differences in rates over time by age group were observed. Owing to the magnitude of differences in male rates by age, they are presented in two separate graphs (Fig. 1a and b). Much less variability in male rates over time in the younger age groups is observed (Fig. 1a). For example, for ages 20–39 years, male rates range from 0 to less than 3 per million, with some evidence of a decline after 1979, when the rates begin to vary around 1 per million. For females in this age group, the rates ranged from 0 to 1 per million with no apparent increasing or decreasing trends over time (Fig. 2).

From ages 40–49 years, male rates showed more variability, with a peak of 13 per million in 1977, but again suggesting an overall decline thereafter to about 3 per million in 2002 (Fig. 1a). The female rates for this age group were relatively flat, ranging from about 1 to 4 per million over time (Fig. 2).

For men aged 50–59 years, the mesothelioma rates were substantially greater than the younger age groups, but relatively stable over time varying around 20 per million, with a suggested decline starting about 1999 to 7 per million in 2002 (Fig. 1b). The rates for women in this age group varied between 2 and 10 per million and converged to 6 per million in 2002, close to the male rate in the same year (Fig. 2).

Table 1 Age-adjusted mesothelioma incidence rates per million persons per year by age group and sex reported in nine SEER registries, 1973–2002^a

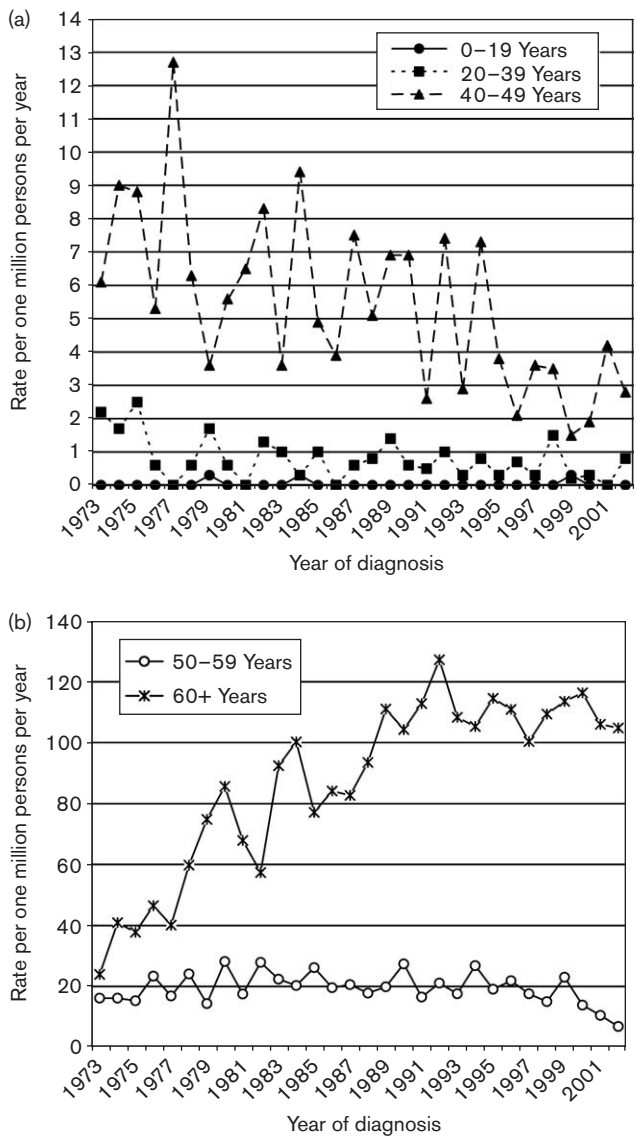
Age group (years)	Male patients		Female patients		Male and female patients	
	Cases	Rate per million	Cases	Rate per million	Cases	Rate per million
Pleural						
0–19	0	0	2	<0.1	2	<0.1
20–39	44	0.4	25	0.2	69	0.3
40–49	181	4.1	66	1.5	247	2.8
50–59	546	16.1	149	4.2	695	10.1
60+	3377	82.2	683	11.5	4060	38.6
All ages ^b	4148	12.2	925	2.6	5073	7.3
Peritoneal						
0–19	0	0	2	<0.1	2	<0.1
20–39	19	0.2	24	0.2	43	0.2
40–49	28	0.6	37	0.8	65	0.7
50–59	69	2.0	49	1.4	118	1.7
60+	243	5.4	176	2.9	419	4.0
All ages ^b	359	1.1	288	0.8	647	0.9
Other sites						
0–19	3	<0.1	1	<0.1	4	<0.1
20–39	11	0.1	12	0.1	23	0.1
40–49	13	0.3	11	0.2	24	0.3
50–59	33	1.0	17	0.5	50	0.7
60+	188	4.7	69	1.2	257	2.5
All ages ^b	248	1.0	110	0.3	358	0.6
Total mesotheliomas (all sites)						
0–19	3	<0.1	5	<0.1	8	<0.1
20–39	74	0.7	61	0.6	135	0.6
40–49	222	5.1	114	2.5	336	3.8
50–59	648	19.1	215	6.0	863	12.4
60+	3808	92.3	928	15.5	4736	46.4
All ages ^b	4755	18.4	1323	3.8	6078	9.8

SEER, National Cancer Institute's Surveillance Epidemiology and End Results.

^aNine SEER registries: New Mexico, Connecticut, Utah, San Francisco-Oakland, Seattle (Puget Sound), Detroit (metropolitan), Atlanta (metropolitan), Iowa, and Hawaii.

^bAge-adjusted rates based on 5-year age groups and standardized (direct method) to the 2000 US population.

Fig. 1

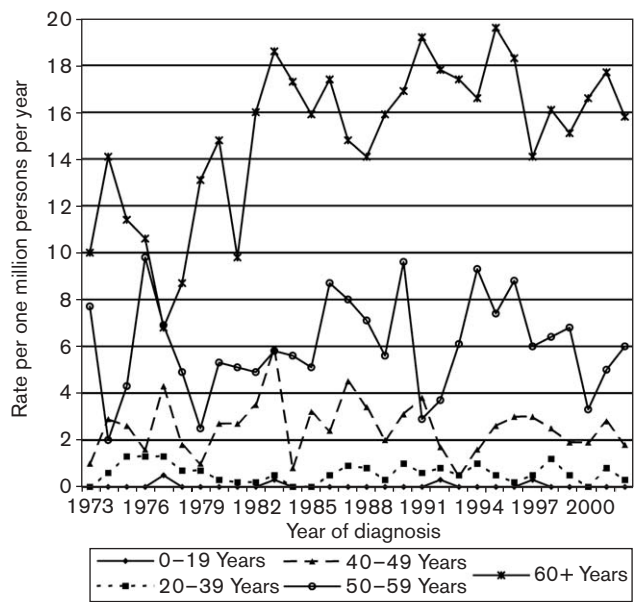


Male mesothelioma (all sites) incidence rates by age group and year of diagnosis for the nine National Cancer Institute's Surveillance Epidemiology and End Results (SEER) registries, 1973-2002 [nine SEER registries: New Mexico, Connecticut, Utah, San Francisco-Oakland, Seattle (Puget Sound), Detroit (metropolitan), Atlanta (metropolitan), Iowa, and Hawaii]. (a) Data for 0-19, 20-39, and 40-49 years. (b) Data for 50-59 and 60+ years.

Men in the oldest age group experienced steep increases from 1973 to 1992, at which point the rates began to decline but remained very high at 105 per million in 2002 (Fig. 1b). Female rates in this age group exhibited less overall variability, ranging from about 10 to 20 per million with a decline after 1995 (Fig. 2).

Since the mid-1970s, the potential for occupational and therefore domestic asbestos exposure would be minimal in the general US population, particularly for exposure to

Fig. 2



Female mesothelioma (all sites) incidence rates by age group and year of diagnosis for the nine National Cancer Institute's Surveillance Epidemiology and End Results (SEER) registries, 1973-2002 [nine SEER registries: New Mexico, Connecticut, Utah, San Francisco-Oakland, Seattle (Puget Sound), Detroit (metropolitan), Atlanta (metropolitan), Iowa, and Hawaii].

amphiboles. The mesothelioma rate in the population who entered the workforce after this time period of reduction of asbestos exposure would provide a reasonable estimate of the background rates of mesothelioma. The annual rate of mesothelioma for males who met these criteria, and were diagnosed at the age of 30 years or above is 1.15 per million (95% CI: 0.90-1.45) (Table 2). For females, the corresponding rate was 0.94 per million (95% CI: 0.71-1.21) (Table 3). The rate for both groups combined was 1.05 per million (95% CI: 0.87-1.24) (data not shown). Therefore, US annual mesothelioma rates for adults under the age 50 years, who would have little or no potential for asbestos exposure, is about 1 per million.

Patterns by anatomical site

Of the 6078 mesothelioma cases in the nine SEER registries, diagnosed from 1973 to 2002, 5073 (83%) cases are pleural, 647 (11%) cases are peritoneal and the remainder are at other anatomical sites (Table 1). As the percentage of mesotheliomas that are pleural is high in males (87%), the pleural rates drive the patterns observed for mesothelioma overall in males. Women have proportionately more cases of peritoneal mesotheliomas (22%) than men (8%). Whereas the male and female peritoneal rates increased with age, there was no obvious pattern by year of diagnosis, with the exception of a

Table 2 Age-adjusted mesothelioma (all sites) incidence rates and 95% confidence limits per million persons per year for males diagnosed at 30 years or older, with year of birth 1953–1972, in 13 SEER registries, 1983–2002^a

Diagnosis year	Birth year																				1953–
	1953	1954	1955	1956	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970	1971	1972	1972
1983–1984																					
Cases	0	0	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
Population	397	207	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	604
Rate	0.00	0.00	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.00
Lower	0.00	0.00	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.00
Upper	9.24	17.76	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6.08
1985–1989																					
Cases	0	0	0	2	0	0	0	–	–	–	–	–	–	–	–	–	–	–	–	–	2
Population	991	1018	1041	837	651	435	219	–	–	–	–	–	–	–	–	–	–	–	–	–	5193
Rate	0.00	0.00	0.00	2.39	0.00	0.00	0.00	–	–	–	–	–	–	–	–	–	–	–	–	–	0.39
Lower	0.00	0.00	0.00	0.27	0.00	0.00	0.00	–	–	–	–	–	–	–	–	–	–	–	–	–	0.04
Upper	3.70	3.60	3.52	8.63	5.63	8.43	16.75	–	–	–	–	–	–	–	–	–	–	–	–	–	1.39
1990–1994																					
Cases	1	2	1	1	3	2	1	0	1	0	0	0	–	–	–	–	–	–	–	–	12
Population	1279	1317	1356	1369	1437	1447	1473	1251	1045	696	352	–	–	–	–	–	–	–	–	–	14 470
Rate	0.78	1.52	0.74	0.73	2.09	1.38	0.69	0.00	0.80	0.00	0.00	–	–	–	–	–	–	–	–	–	0.83
Lower	0.01	0.17	0.01	0.01	0.42	0.16	0.01	0.00	0.01	0.00	0.00	–	–	–	–	–	–	–	–	–	0.43
Upper	4.35	5.48	4.10	4.06	6.10	4.99	3.84	2.49	4.45	3.51	5.27	10.43	–	–	–	–	–	–	–	–	1.45
1995–1999																					
Cases	3	4	1	2	3	3	3	2	2	1	0	1	1	0	2	0	0	–	–	–	28
Population	1416	1464	1520	1552	1610	1623	1636	1677	1694	1704	1700	1688	1655	1279	954	637	335	–	–	–	24 144
Rate	2.12	2.73	0.66	1.29	1.86	1.85	1.83	1.19	1.18	0.59	0.00	0.59	0.60	0.00	2.10	0.00	0.00	–	–	–	1.16
Lower	0.43	0.74	0.01	0.14	0.37	0.37	0.37	0.13	0.13	0.01	0.00	0.01	0.01	0.00	0.24	0.00	0.00	–	–	–	0.77
Upper	6.19	7.00	3.66	4.65	5.45	5.40	5.36	4.31	4.26	3.27	2.16	3.30	3.36	2.87	7.57	5.76	10.96	–	–	–	1.68
2000–2002																					
Cases	2	1	4	5	2	4	2	1	1	1	1	1	0	0	2	1	1	0	1	0	30
Population	831	862	909	908	927	951	954	1012	978	986	980	993	999	940	916	934	958	1023	647	309	18 019
Rate	2.41	1.16	4.40	5.51	2.16	4.20	2.10	0.99	1.02	1.01	1.02	1.01	0.00	0.00	2.18	1.07	1.04	0.00	1.54	0.00	1.66
Lower	0.27	0.02	1.18	1.77	0.24	1.13	0.24	0.01	0.01	0.01	0.01	0.01	0.00	0.00	0.25	0.01	0.01	0.00	0.02	0.00	1.12
Upper	8.69	6.46	11.26	12.85	7.79	10.77	7.57	5.50	5.69	5.64	5.68	5.60	3.67	3.90	7.88	5.95	5.81	3.59	8.60	11.86	2.38
Total: 1983–2002																					
Cases	6	7	6	10	8	9	6	3	4	2	1	2	1	0	4	1	1	0	1	0	72
Population	4914	4866	4827	4666	4626	4456	4256	4163	3923	3735	3377	3032	2653	2219	1871	1571	1293	1023	647	309	62 430
Rate	1.22	1.44	1.24	2.14	1.73	2.02	1.41	0.72	1.02	0.54	0.30	0.66	0.38	0.00	2.14	0.64	0.77	0.00	1.54	0.00	1.15
Lower	0.45	0.58	0.45	1.03	0.74	0.92	0.51	0.14	0.27	0.06	0.00	0.07	0.00	0.00	0.58	0.01	0.01	0.00	0.02	0.00	0.90
Upper	2.66	2.96	2.71	3.94	3.41	3.83	3.07	2.11	2.61	1.93	1.65	2.38	2.10	1.65	5.47	3.54	4.30	3.59	8.60	11.86	1.45

SEER, National Cancer Institute's Surveillance Epidemiology and End Results.

^a13 SEER registries: New Mexico, Connecticut, Utah, San Francisco–Oakland, Seattle (Puget Sound), Detroit (metropolitan), Atlanta (metropolitan), Iowa, Hawaii, San Jose/Monterey, Los Angeles, Georgia (rural), and Alaska Native Registry.

Table 3 Age-adjusted mesothelioma (all sites) incidence rates and 95% confidence limits per million persons per year for females diagnosed at 30 years or older, with year of birth 1953–1972, in 13 SEER registries, 1983–2002^a

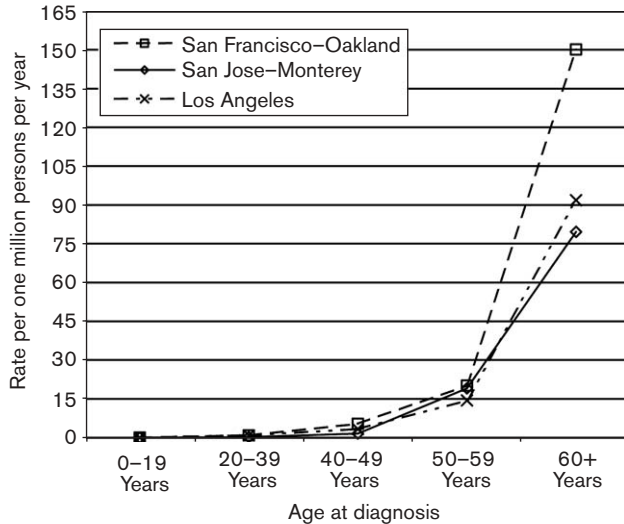
Diagnosis year	Birth year																				1953–
	1953	1954	1955	1956	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970	1971	1972	1972
1983–1984																					
Cases	0	0	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
Population	400	207	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	608
Rate	0.00	0.00	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.00
Lower	0.00	0.00	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.00
Upper	9.16	17.68	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6.04
1985–1989																					
Cases	0	0	1	0	1	0	0	–	–	–	–	–	–	–	–	–	–	–	–	–	2
Population	1003	1030	1049	845	654	437	220	–	–	–	–	–	–	–	–	–	–	–	–	–	5237
Rate	0.00	0.00	0.95	0.00	1.53	0.00	0.00	–	–	–	–	–	–	–	–	–	–	–	–	–	0.38
Lower	0.00	0.00	0.01	0.00	0.02	0.00	0.00	–	–	–	–	–	–	–	–	–	–	–	–	–	0.04
Upper	3.66	3.56	5.30	4.34	8.51	8.40	16.70	–	–	–	–	–	–	–	–	–	–	–	–	–	1.38
1990–1994																					
Cases	1	3	0	4	2	1	0	2	1	1	0	0	–	–	–	–	–	–	–	–	15
Population	1293	1324	1355	1368	1425	1429	1427	1446	1224	1011	673	339	–	–	–	–	–	–	–	–	14 314
Rate	0.77	2.27	0.00	2.92	1.40	0.70	0.00	1.38	0.82	0.99	0.00	0.00	–	–	–	–	–	–	–	–	1.05
Lower	0.01	0.46	0.00	0.79	0.16	0.01	0.00	0.16	0.01	0.01	0.00	0.00	–	–	–	–	–	–	–	–	0.59
Upper	4.30	6.62	2.71	7.49	5.07	3.89	2.57	5.00	4.55	5.50	5.45	10.82	–	–	–	–	–	–	–	–	1.73
1995–1999																					
Cases	2	3	1	3	1	0	1	2	0	1	1	2	3	1	0	0	0	–	–	–	21
Population	1447	1490	1536	1566	1606	1614	1624	1664	1664	1655	1637	1637	1606	1241	924	614	320	–	–	–	23 862
Rate	1.38	2.01	0.65	1.92	0.62	0.00	0.62	1.21	0.00	0.60	0.60	1.22	1.87	0.81	0.00	0.00	0.00	–	–	–	0.88
Lower	0.16	0.40	0.01	0.39	0.01	0.00	0.01	0.14	0.00	0.01	0.01	0.14	0.38	0.01	0.00	0.00	0.00	–	–	–	0.54
Upper	4.99	5.88	3.62	5.60	3.46	2.27	3.43	4.37	2.20	3.34	3.36	4.41	5.46	4.48	3.97	5.97	11.47	–	–	–	1.35
2000–2002																					
Cases	2	2	4	2	0	5	1	2	0	0	1	1	0	0	0	0	0	0	0	0	20
Population	860	885	923	927	941	958	956	1001	977	975	972	977	965	912	893	899	925	979	625	299	17 849
Rate	2.32	2.26	4.33	2.16	0.00	5.22	1.05	2.00	0.00	0.00	1.03	1.02	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.12
Lower	0.26	0.25	1.17	0.24	0.00	1.68	0.01	0.22	0.00	0.00	0.01	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.68
Upper	8.39	8.16	11.09	7.79	3.90	12.18	5.82	7.22	3.76	3.76	5.73	5.69	3.80	4.02	4.11	4.08	3.97	3.75	5.87	12.26	1.73
Total: 1983–2002																					
Cases	5	8	6	9	4	6	2	6	1	2	2	3	3	1	0	0	0	0	0	0	58
Population	5004	4937	4864	4706	4626	4437	4227	4099	3865	3650	3300	2953	2571	2153	1817	1514	1244	979	625	299	61 869
Rate	1.00	1.62	1.23	1.91	0.86	1.35	0.47	1.46	0.26	0.55	0.61	1.02	1.17	0.46	0.00	0.00	0.00	0.00	0.00	0.00	0.94
Lower	0.32	0.70	0.45	0.87	0.23	0.49	0.05	0.53	0.00	0.06	0.07	0.20	0.23	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.71
Upper	2.33	3.19	2.68	3.63	2.21	2.94	1.71	3.19	1.44	1.98	2.19	2.97	3.41	2.58	2.02	2.42	2.95	3.75	5.87	12.26	1.21

SEER, National Cancer Institute's Surveillance Epidemiology and End Results.

^a13 SEER Registries: New Mexico, Connecticut, Utah, San Francisco–Oakland, Seattle (Puget Sound), Detroit (metropolitan), Atlanta (metropolitan), Iowa, Hawaii, San Jose/Monterey, Los Angeles, Georgia (rural), and Alaska Native Registry.

suggested decline since the late 1990s in the over 39-year-old groups (data not shown). Adult male and female rates for peritoneal mesothelioma were similar for ages under 40 years; females had slightly higher rates in the 40–49-year-old group, whereas males exceeded females in the oldest ages, particularly in the 60+ years group (5.4 vs. 2.9 per million).

Fig. 3



Male mesothelioma (all sites) average annual incidence rates by age of diagnosis for three California National Cancer Institute's Surveillance Epidemiology and End Results (SEER) registries, 1992–2002 (three California SEER registries: San Francisco–Oakland, San Jose–Monterey, Los Angeles).

California comparisons

We compared mesothelioma rates from the three CA SEER registries – San Francisco–Oakland (SFO), San Jose–Monterey (SJM), and Los Angeles – with each other and with the remaining SEER registries for the years 1992–2002. We examined the latter relationship both with and without the Seattle SEER population, which employed nearly 100 000 shipyard workers at peak employment in 1943 (Blot *et al.*, 1979).

For males over 19- years of age, SFO rates exceeded those of the other two regions (Fig. 3). For the 50–59-year-old age group, both SFO and SJM had higher rates than Los Angeles. For the oldest age group, 60+ years; the SFO rate per million (150) clearly exceeded the rates for SJM (80); and Los Angeles (92).

The male mesothelioma rates for SFO were also greater than those of the remaining eight non-CA SEER regions for all age groups over 19 years, but were significantly greater only for the oldest age group [relative risk (RR) = 1.5; 95% CI: 1.28–1.59] (Table 4). With the exclusion of Seattle from the comparison group, the rate ratio for the oldest age group increased to 1.8 (95% CI: 1.51–1.90). Seattle male rates were 70–100% higher than the other seven SEER registries, excluding California registries, in the two oldest age groups, but were comparable for the younger age groups (data not shown).

Combining the three California male populations and comparing them with the remaining eight SEER registries outside of California, we observed no meaningful

Table 4 Age-adjusted mesothelioma (all sites) incidence rates per million persons per year and incidence rate ratios by age group for California males and females versus seven or eight SEER registries, 1992–2002

Male patients				Female patients			
Rate ratio	95% confidence limits	California population	SEER population	Rate ratio	95% confidence limits	California population	SEER population
San Francisco–Oakland to eight SEER registries ^a (years)							
20–39	1.8	0.86–4.99	7 393 205	0.5	0.11–1.91	7 072 052	36 705 492
40–49	1.6	0.93–2.68	3 431 654	0.7	0.33–1.83	3 434 351	18 221 027
50–59	1.2	0.89–1.69	2 302 155	1.3	0.76–2.12	2 390 716	12 432 549
60+	1.5*	1.28–1.59	2 910 312	1.3*	1.00–1.62	3 906 775	21 147 573
San Francisco–Oakland to seven SEER registries ^b							
20–39	2.3	0.88–5.53	7 393 205	0.4	0.10–1.82	7 072 052	30 152 794
40–49	1.5	0.85–2.47	3 431 654	0.8	0.34–1.93	3 434 351	14 792 153
50–59	1.4	0.99–1.92	2 302 155	1.3	0.78–2.24	2 390 716	10 181 175
60+	1.8*	1.51–1.90	2 910 312	1.5*	1.14–1.88	3 906 775	17 653 210
Three California registries ^c to eight SEER registries							
20–39	1.6	0.91–3.18	29 598 602	0.5	0.24–1.11	27 879 747	36 705 492
40–49	1.1	0.73–1.60	12 218 337	0.9	0.57–1.53	12 327 923	18 221 027
50–59	1.0	0.82–1.28	7 891 596	1.0	0.73–1.49	8 356 044	12 432 549
60+	1.0	0.94–1.10	9 976 905	1.2	0.98–1.35	13 398 263	21 147 573
San Jose–Monterey + Los Angeles to seven SEER registries ^b							
20–39	1.8	0.81–3.49	4 566 237	0.4	0.21–1.20	4 022 220	30 152 794
40–49	0.8	0.51–1.31	1 910 326	1.0	0.59–1.82	1 833 853	14 792 153
50–59	1.1	0.81–1.39	1 212 030	1.0	0.66–1.53	1 235 684	10 181 175
60+	1.0	0.91–1.12	1 417 091	1.3*	1.04–1.53	1 855 171	17 653 210

SEER, National Cancer Institute's Surveillance Epidemiology and End Results.

^aEight SEER registries: New Mexico, Connecticut, Utah, Seattle (Puget Sound), Detroit (metropolitan), Atlanta (metropolitan), Iowa, and Hawaii.

^bSeven SEER registries: New Mexico, Connecticut, Utah, Detroit (metropolitan), Atlanta (metropolitan), Iowa, and Hawaii.

^cThree California SEER registries: San Francisco/Oakland, San Jose/Monterey, Los Angeles.

**P* < 0.05.

difference in rates, with rate ratios of 1.6 (20–39 years), 1.1 (40–49 years), 1.0 (50–59 years), and 1.0 (60+ years) (Table 4). This comparison included the two shipyard regions, SFO among the three populations of California and Seattle in the comparison group. With complete removal of these two regions, the rate ratios for SJM and LA males compared with seven SEER registries were 1.8 (20–39 years), 0.8 (40–49 years), 1.1 (50–59 years), and 1.0 (60+ years).

The rates for females in the three SEER registries in California increased with age but exhibited no clear pattern of differences among them, with the exception that Los Angeles had lower rates than the other two in the oldest age groups (Fig. 4). When the three regions combined were compared with the remaining SEER populations, only the 60+ years female age group had a higher mesothelioma rate, with a rate ratio of 1.2 (95% CI: 0.98–1.35) (Table 4). The rate ratio for SFO females in the oldest age group, compared with rest of SEER (excluding Seattle) was 1.5 (95% CI: 1.14–1.88), a statistically significant difference. Seattle females had higher mesothelioma rates in every adult age group than females in SFO and in the other seven SEER registries. With the exclusion of SFO and Seattle from the comparison group, the remaining two California SEER

registries had statistically significantly higher female rates in the oldest age group (18 per million) than for the rest of SEER (14 per million) for a rate ratio of 1.3 (95% CI: 1.04–1.53).

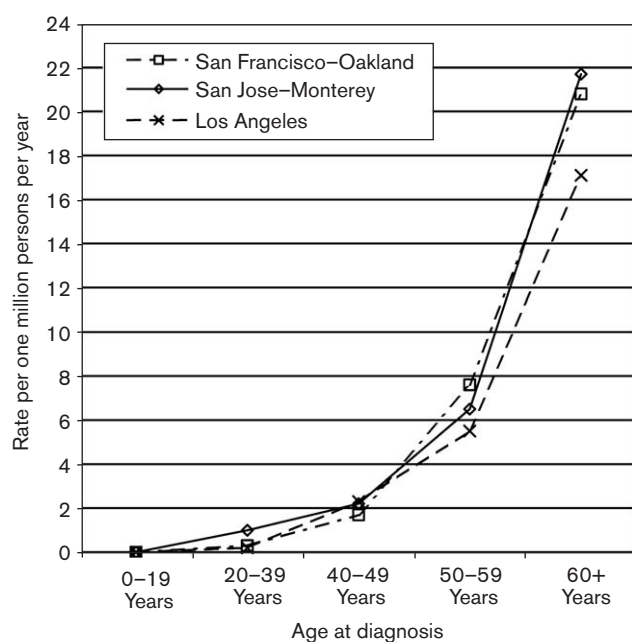
Discussion

A number of studies have been published examining mesothelioma rates over time using incidence data from the SEER program (Spirtas *et al.*, 1986; McDonald and McDonald, 1994; Hankey *et al.*, 1999). Several analyses were focused on future predictions and observed that rates seemed to be decreasing in the United States in recent years, consistent with the long latency period for this disease, and the decline in asbestos use over the past 30–40 years (Walker *et al.*, 1983; Price, 1997; Weill *et al.*, 2004). Consistent with earlier reports, we observed the following incidence patterns for the time period 1973–2002: (i) rates among males over the age of 50 years greatly exceeded female rates, (ii) rates increased with age for males and females, (iii) steep increases in the oldest age groups for males and females, (iv) much less variability in female rates, and these rates were relatively flat under the age of 60, (v) rates in the older age groups for both males and females showed signs of declining since the late 1990s, and (vi) there were proportionately more cases of peritoneal mesothelioma among females. As women have less opportunity for substantial amphibole exposures, the generally accepted asbestos cause of peritoneal mesothelioma, the higher female peritoneal to total mesothelioma ratio suggests misdiagnosis or more likely a higher background rate, unrelated to asbestos.

The majority of trend analyses in the literature use age-adjusted rates that summarize over different age groups, therefore, producing an overall pattern; for example, a pattern that pleural mesothelioma rates seem to be increasing. By using sex and age-specific rates (within categories), we were able to demonstrate that the older age groups drive this pattern, whereas rates for younger age groups are relatively flat. Second, we were able to demonstrate interesting and new male/female similarities and differences. For example, rates for ages 20–39 years are similar for the two sexes, and for ages 50–59 years, recent rates of males and females begin to converge at around 6 per million. Again in age-adjusted analyses, the approach most often presented in the literature male/female ratio is much greater than 1.0 because it is dominated by the oldest age group. The different underlying patterns are revealed by age-specific rate comparisons.

Archer and Rom (1983) reported differences by age in an examination of pleural mesothelioma mortality trends from 1958 to 1977. They reported similar rates for males and females below the age of 45 years, at which point the two diverge with male rates increasing sharply, and noted

Fig. 4



Female mesothelioma (all sites) average annual incidence rates by age at diagnosis for three California National Cancer Institute's Surveillance Epidemiology and End Results (SEER) registries, 1992–2002 (Three California SEER registries: San Francisco–Oakland, San Jose–Monterey, Los Angeles).

the usefulness of examining age-specific and sex-specific rates.

Our results also illustrate the informative value of examining incidence rates by age groups, rather than averaged over all ages, for purposes of estimating background rates of mesothelioma. Furthermore, we provide an alternative approach by removing, to the extent possible, the impact of asbestos exposure in both men and women by restricting rates to adults who entered the workforce after 1972.

Although the data are analyzed by age, time period, and sex, we are unable to correlate changes in mesothelioma rates to specific levels and types of asbestos exposure, as might be feasible if one had access to a major longitudinal cohort study that included participants who were hired after asbestos usage declined. Furthermore, sparse numbers in the youngest age groups did not permit a formal age-period-cohort analysis. Nevertheless, we were able to conduct analyses without such modeling by use of restriction, as described above. In Tables 2 and 3, we restrict mesothelioma rates to the 1953–1972 birth cohort and to diagnoses made in 1983–2002, which fixes age to be 30–50 years at diagnosis. This permits an examination of rates for men and women who were unlikely to have experienced asbestos exposure and therefore are demonstrating a background rate for this age group of about 1 per million, similar to the estimate of McDonald and McDonald (1985). Whereas McDonald (1985) examined rates before the onset of asbestos-related diseases to estimate background, we examined rates that represent background upon the termination of asbestos exposures. The slightly higher estimated background rates in males may be because of residual occupational asbestos exposure, such as remodeling of old homes, replacement of old furnaces, or demolition work without following safe work practices after 1972. The background rates for those under the age of 30 years seem to be well under 1 per million, suggesting increasing background rates with age.

Using our approach, however, we were unable to estimate how much greater background rates might be for those over the age of 50 years, because at this point in time, the influence of past occupational and domestic exposure for the older populations cannot be removed. Determination of whether the background rate of mesothelioma at older ages (50+ years) is also about 1 per million or perhaps greater because of susceptibility of an ageing population must await future SEER statistics.

Price and Ware (2004) contributed to the literature by addressing threshold exposure and background rates. They argued that stable female rates are consistent with the existence of a threshold exposure, as women have had predominately environmental and domestic exposures that have increased over time; however, the age-adjusted

rates did not increase. Assuming all cases in female patients are unrelated to asbestos exposure, these authors suggested an annual background rate for mesothelioma in females of 4 per million. They cautiously noted that their estimates might be at the upper bounds, if some of the cases in female patients were due to occupational or environmental asbestos exposure.

Our evaluation of mesothelioma rates by age groups, rather than overall age-adjusted rates permitted us to identify the stable female rates in the younger age groups, and conclude that incidence patterns differed from the older age groups, among whom occupational and possibly environmental asbestos exposures may have influenced rates.

It seems that the older women, particularly the 60+ year-old group, had increasing rates from about 1977 through the late 1980s, followed by an apparent decline around 1992. This may be explained, in part, by the number of women working in shipyards and other industrial jobs during World War II. For example, women accounted for 20–27% of the workforce in some shipyards in the San Francisco area (National Park Service, 2006).

Numerous studies have documented the high risk of mesothelioma because of shipyard asbestos exposures from 1934 through about 1975, when amphiboles were no longer used for insulation in Navy vessels (Fleischer *et al.*, 1946; Fisher, 1998, 2001; Rushworth, 2005). The presence of a major shipyard in the SFO region has likely influenced the mesothelioma rates in this region. SFO male rates exceeded those of the other two SEER registries in California and the remaining eight SEER registries outside of California combined for all adult age groups examined, particularly for the 60+ years age group, whose average annual mesothelioma rate from 1992 to 2002 was 150 per million in the SFO region. Female rates in the SFO region compared with the rest of SEER, excluding Seattle, were higher only in the 60+ years age group. The male and female rates for the Seattle SEER region exceeded all other SEER regions combined, and SFO for the two oldest age groups. The elevated rates for older women may be a result of employment in the Seattle area shipyards, and/or domestic exposure from their spouses who worked there during the period of extensive use of asbestos insulation.

The three California SEER registries' male mesothelioma rates differed little from the remaining eight SEER registries, which included Seattle. After the shipyard regions were excluded from the comparisons, there were no meaningful differences among men by age. Female rates in the oldest age group, however, were slightly higher in these two California regions. This may be related to the fact that during World War II, the Western

United States had the highest percentage of female industrial workers in the country, not only in shipyards but also in a wide variety of defense jobs (Archer and Rom, 1983).

Given the estimated 3300 cases of mesothelioma per year in the US population of approximately 300 million (US Cancer Statistics Working Group, 2006; US Census Bureau, 2006), upwards of 300 (1 per million) annually may be unrelated to asbestos exposure. Cases unrelated to asbestos exposure may reflect spontaneous cases, a small proportion of cases because of therapeutic radiation (Teta *et al.*, 2007), and/or cases because of unrecognized causes. Additional research is required to elucidate additional causes of this disease.

Acknowledgements

This study was supported by funding from Daimler-Chrysler Corporation, Ford Motor Company, and General Motors Corporation. One of us (M.J.T.) has served as an expert witness in litigation regarding the potential health hazards of asbestos to mechanics historically involved in vehicle repair.

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EXHIBIT 11

Projection of mesothelioma mortality in Britain using Bayesian methods

E Tan^{*,1}, N Warren¹, AJ Darnton² and JT Hodgson²

¹Health and Safety Laboratory, Harpur Hill, Buxton, Derbyshire SK17 9JN, UK; ²Epidemiology Unit, Health and Safety Executive, Redgrave Court, Merton Road, Bootle, Merseyside L20 7HS, UK

BACKGROUND: Mesothelioma mortality has increased more than ten-fold over the past 40 years in Great Britain, with > 1700 male deaths recorded in the British mesothelioma register in 2006. Annual mesothelioma deaths now account for > 1% of all cancer deaths. A Poisson regression model based on a previous work by Hodgson *et al* has been fitted, which has allowed informed statistical inferences about model parameters and predictions of future mesothelioma mortality to be made.

METHODS: In the Poisson regression model, the mesothelioma risk of an individual depends on the average collective asbestos dose for the individual in a given year and an age-specific exposure potential. The model has been fitted to the data within a Bayesian framework using the Metropolis–Hastings algorithm, a Markov Chain Monte Carlo technique, providing credible intervals for model parameters as well as prediction intervals for the number of future cases of mortality.

RESULTS: Males were most likely to have been exposed to asbestos between the ages of 30 and 49 years, with the peak year of asbestos exposure estimated to be 1963. The estimated number of background cases was 1.08 cases per million population.

CONCLUSION: Mortality among males is predicted to peak at approximately 2040 deaths in the year 2016, with a rapid decline thereafter. Approximately 91 000 deaths are predicted to occur from 1968 to 2050 with around 61 000 of these occurring from 2007 onwards.

British Journal of Cancer (2010) 103, 430–436. doi:10.1038/sj.bjc.6605781 www.bjcancer.com

Published online 13 July 2010

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Keywords: mesothelioma; mortality; Great Britain; Bayesian; Markov Chain Monte Carlo

Mesothelioma is a cancer that mainly affects the pleura (the membrane that covers the lungs and lines the internal chest wall) and the peritoneum (the membrane that forms the lining of the abdominal cavity). Of all deaths, 85% have been among men and the majority of these were caused by occupational exposure to asbestos fibres (Rake *et al*, 2009). The disease has a long latency period; symptoms usually emerge between 15 and 60 years after exposure to asbestos, after which mesothelioma is rapidly fatal. The majority of deaths occur among those > 60 years of age, with few deaths occurring among those < 50 years. Although the majority of cases of mesothelioma are caused by exposure to asbestos, much of which occurred in occupational settings, particularly among men, a small number of cases occur spontaneously among those with no history of exposure. Annual mesothelioma deaths have increased more than ten-fold over the past 40 years and now account for > 1% of all cancer deaths.

Predictions of mesothelioma mortality have been made in several countries. Clements *et al* (2007) modelled mesothelioma mortality in Australia using both an age–birth cohort model and a model based on that introduced by Hodgson *et al* (2005). Banaei *et al* (2000) predicted mortality in France using a method based on a risk function that links mortality with past exposure to asbestos.

Segura *et al* (2003) used an age–period–cohort model to predict mortality in the Netherlands. Hodgson *et al* (2005) developed a model based on the estimated collective population exposure to asbestos and a specific form for the relationship between mesothelioma risk and time since first exposure at the population level. The model was fitted to mesothelioma mortality for Great Britain up to 2001 and projections of mortality were made by applying fitted mesothelioma rates to future population projections. Confidence intervals for the parameters and prediction intervals for future estimated annual deaths could not be made because of limitations in the optimisation approach adopted. This paper presents the results of a Bayesian statistical analysis to refit a modified version of this model using updated mortality data up to 2006 and a Markov Chain Monte Carlo (MCMC) method of computation. The Bayesian approach allowed credible and prediction intervals to be calculated; thus, informed statistical inferences about model parameters and predictions of future mortality, in particular the scale and timing of the peak in deaths, could be made.

MATERIALS AND METHODS

The model

The British Mesothelioma Register contains all deaths in Great Britain since 1968 in which mesothelioma was mentioned on the

*Correspondence: Dr E Tan; E-mail: emma.tan@hsl.gov.uk

Received 15 March 2010; revised 10 May 2010; accepted 16 June 2010; published online 13 July 2010

death certificate. It provides the basis for a consistent data series of mesothelioma mortality over nearly four decades. In both males and females, 99% of all these deaths are among those between the ages of 20 and 89 years. The data used in the analyses carried out in this report are based on deaths of males aged 20–89 years, between 1968 and 2006. The model developed by Hodgson *et al* (2005) is based on that developed by the Health Effects Institute (1991). In brief, the Health Effects Institute (1991) model, in which an individual's mesothelioma risk is assumed to be proportional to the increase in cumulative exposure multiplied by a power of time since exposure lagged by 10 years, was applied at the population level; this was achieved by assuming that the average asbestos exposure for males in Great Britain in each year can be summarised by a single estimate and that their exposure in any given year also depends on their age. Parameters to model change in completeness of mesothelioma diagnosis over time and the clearance half-life of asbestos fibres in the lungs were also included. Allowance for a background rate of mesotheliomas not caused by asbestos exposure was not originally included by Hodgson *et al* (2005); however, background cases may account for a higher proportion of deaths in certain years and among the most recent birth cohorts, and we have included a term to allow for such cases in the modified version of the model that can be represented as follows:

$$\lambda_{A,T} = \frac{\left[\sum_{l=1}^{A-1} W_{A-l} D_{T-l} \{l+1-L\}^k 0.5^{l/H} I_l \right] D_{x_T} P_{A,T} \left(M - \sum_{A,T} B_{A,T} \right)}{\sum_{A,T} \left[\sum_{l=1}^{A-1} W_{A-l} D_{T-l} \{l+1-L\}^k 0.5^{l/H} I_l \right] D_{x_T} P_{A,T}} + B_{A,T} \quad (1)$$

where $\lambda_{A,T}$ is the number of deaths at age A in year T , W_A is the overall age-specific exposure potential at age A , D_T is the overall population exposure in year T , D_{x_T} is the proportion of mesothelioma deaths in year T that are recorded, L is the lag period in years between exposure and disease occurrence, H is the half-life in years for asbestos clearance from the lungs, k is the power of time representing the increase of risk with increase of time since exposure, $P_{A,T}$ is the person-years at risk for age A in year T , M is the total observed mesothelioma deaths from 1968 to 2006, I is an indicator variable where $I=0$ if $l < L-1$ and $I=1$ otherwise, l indexes years lagged from the risk year and $B_{A,T}$ is the number of background cases for age A at year T .

Modelling technique

The model was originally fitted by Hodgson *et al* (2005) using a manual iterative approach to minimising the model deviance. In this case, the deviance can be expressed as

$$D = 2 \sum_{A,T} \left[Y_{A,T} \log \left(\frac{Y_{A,T}}{\hat{\lambda}_{A,T}} \right) - \left(Y_{A,T} - \hat{\lambda}_{A,T} \right) \right], \quad (2)$$

where $Y_{A,T}$ are the observations and $\lambda_{A,T}$ are the fitted values. However, confidence intervals for both the parameter estimates and predictions of mortality could only be obtained using an informal numerical approach rather than analytically. We used a more refined statistical analysis using the Metropolis–Hastings algorithm (Metropolis *et al*, 1953; Hastings, 1970), an MCMC method. This method allows not only model parameters to be estimated, but also Bayesian credibility intervals to be easily obtained using formal statistical methods, which is the main advantage of adopting a Bayesian approach. Because of the number of parameters and the complexity of the model, it would have been difficult to adopt a frequentist approach to obtain parameter estimates and confidence intervals.

Model parameters

- (i) The age-specific exposure potential, W_A , allowed the exposure of males in a given year to vary by age. Nine parameters were assigned to W_A , representing the exposure weighting for the age groups 0–4, 5–15, 16–19, 20–29, 30–39, 40–49, 50–59, 60–64 and 65+, with the age group 20–29 years chosen as the baseline category.
- (ii) The overall population exposure, D_T , represents the average 'effective carcinogenic dose' in the breathing zone of men aged 20–89 years and is included as a unit-free parameter vector in the model. The shape of the exposure curve and the change in exposure levels over time is the main interest in the inclusion of D_T . D_T was defined by growth and decline rates for years in multiples of 10 before and after the maximum exposure year, called *Peakyear* (at which the gradient of the exposure curve is zero). The growth rates for intermediate years were determined by linear interpolation. The set of growth rates at *Peakyear* – 65, *Peakyear* – 55, *Peakyear* – 45, *Peakyear* – 35, *Peakyear* – 25, *Peakyear* – 15, *Peakyear* – 5, *Peakyear* + 5 and *Peakyear* + 15 was included as a multivariate parameter in the model. Parameters defining the exposure distribution in the most recent years could not be estimated because of the long latency period of mesothelioma; instead, assumptions about the level of exposure from the year 2000 based on the HSE Regulatory Impact Assessment (HSE, 2002) were used as in Hodgson *et al* (2005). From the year 2000 onwards, it was assumed that the total asbestos exposure to the population would be approximately 4% of the peak value in 2000, 2% in 2010 and 0.75% in 2050. Between the last year for which the growth rate was estimated and 2000, the value of the exposure was determined by linear interpolation.
- (iii) The diagnostic trend D_{x_T} was defined by a parameter α , representing the annual percentage decrease in the number of missed cases, working backwards in time from 1997, in which diagnosis was assumed to be essentially complete (98%).
- (iv) The background rate is represented by the number of cases per million in the male population. The age distribution of the background cases in each year is assumed to be $(A-L)^k$. The proportion of background cases at age A in each year is therefore assumed to be $(A-L)^k / \sum_A (A-L)^k$.

Population projections

To obtain mesothelioma mortality projections from 2007 to 2050, population projections of the number of males aged between 20 and 89 at every year between 2007 and 2050 were obtained from the Office for National Statistics.

The model

From a Bayesian perspective, the parameters of a statistical model are considered random quantities. Bayesian inference can usually be summarised by random draws from the posterior distributions of the model parameters. Let $\text{Lik}(Y|\theta)$ be the likelihood function of the data Y , θ be the vector of model parameters and $\phi(\theta)$ be the prior distribution of the parameters, which represents the prior information we have on θ . The posterior distribution $\pi(\theta)$ of θ is

$$\pi(\theta) \propto \text{Lik}(Y|\theta) \phi(\theta). \quad (3)$$

Assuming that the observations follow a Poisson distribution, the likelihood function is

$$\text{Lik}(Y|\theta) = \prod_{A,T} \left(\frac{e^{-\lambda_{A,T}} \lambda_{A,T}^{Y_{A,T}}}{Y_{A,T}!} \right) \quad (4)$$

which is the product of the individual likelihood contributions for each observation over all ages and years of death. We assumed that all possible parameter values within a chosen interval were equally likely by using uniform prior distributions. The intervals were chosen by considering the maximum plausible ranges, taking into account the results of Hodgson *et al* (2005).

Statistical inference

Unfortunately, because of the complexity of the likelihood, the posterior distribution is unavailable in closed form. Numerical techniques, particularly MCMC, are thus required to evaluate the posterior distribution. Thus, MCMC techniques require simulation to generate random samples from a complex posterior distribution. We generated 35 000 sets of random draws from the joint posterior distribution of the model parameters after a burn-in of 20 000 iterations to minimise the effect of initial values on posterior inference. After the burn-in period, the empirical distributions should eventually approximate the true shapes of the posterior distributions closely. Point estimates and credible intervals are then calculated from this distribution.

Proposal distributions

Apart from the proposal distribution for *Peakeyear*, each distribution was chosen to be normal with s.d. such that the acceptance probability ranged between 20 and 45%. It should be noted that the proposal distributions do not have an effect on the posterior parameter estimates, but only on the convergence, mixing and autocorrelation of the chains generated by the Metropolis–Hastings algorithm. The Metropolis–Hastings algorithm was implemented in Matlab (The MathsWorks, Inc., Natick, MA, USA; 2008).

Prior distributions

Non-informative prior distributions for each parameter were chosen by considering plausible ranges, taking into account the results in Hodgson *et al* (2005). In the previous analysis, *k* has been estimated at between 2 and 3. It was unlikely that the risk decreased with time since exposure, and hence the prior for *k* was chosen to be $U(0, 10)$. Each of the *W* parameters represents age-specific exposure potential and can only take positive values. It was considered unlikely that the risk in any of the age groups was 10 times greater than that of males aged 20–29 years (the baseline age group), and hence the priors for *W* were chosen to be $U(0, 10)$. Each of the *D* parameters represents the growth rates of population exposure levels. As the overall population exposure can only take positive values the decline rate must not exceed 100%, and hence the lower bound for *D* must be -100 . Taking into account the data on asbestos imports as well as the levels of asbestos use in Great Britain, the peak year of exposure was assumed to be between 1950 and 2000, and hence the prior distribution of *Peakeyear* was chosen to be uniformly distributed on integer values between 1950 and 2000. By definition, the background rate can only take positive values. Hodgson *et al* (2005) suggest that a background rate of 1 to 2% of total mesothelioma deaths, equating to approximately 25–50 male deaths annually, is widely assumed. A uniform $U(0, 20)$ prior was chosen for α (cases per million). As a result of problems encountered when attempting to estimate *H*, various prior distributions for *H* were considered. Table 1 shows the prior distributions that were used.

RESULTS

The parameter estimates are shown in Table 2. The parameter *L* was fixed at 10, as in Hodgson *et al* (2005).

Table 1 Prior distributions for model parameters

Parameter	Prior
<i>H</i>	Various
<i>k</i>	$U(0, 10)$
$W_k \forall k$	$U(0, 10)$
$D_k \forall k$	$U(-100, 200)$
α	$U(-0.07, 0.09)$
<i>Peakeyear</i>	$U(1950, 2000)$
<i>Rate</i>	$U(0, 20)$

Table 2 Parameter estimates from fitting Poisson regression model

Parameter	Metropolis–Hastings Posterior median (90% CI)	Hodgson <i>et al</i> (2005) Estimate
Power of time since exposure, <i>k</i>	2.42 (2.28, 2.56)	2.6
Background rate, <i>Rate</i> (per million)	1.08 (0.71, 1.51)	—
Maximum exposure year, <i>Peakeyear</i>	1963	1967
Clearance half-life, <i>H</i> (years)	1 000 000 (fixed)	1000 (fixed)
Diagnostic trend, α (%)	—	5
<i>Change in exposure index (percentage per year) in peak year $\pm X$ years</i>		
–65	0 (fixed)	—
–55	1000 (fixed)	—
–45	100 000 (fixed)	29
–35	–91.3 (–98.2, –50.1)	6
–25	104.6 (44.8, 135.5)	11
–15	–25.5 (–34.9, –8.28)	9
–5	36.6 (23.2, 47.8)	5
0 (Peak year)	0 (by definition)	0 (by definition)
5	–7.5 (–14.1, –1.4)	–14
15	–18.6 (–27.5, –8.8)	–39
<i>Relative exposure potential for age group (years)</i>		
0–4	0.0019 (0.0001, 0.0074)	0.00
5–15	0.0023 (0.0002, 0.0091)	0.03
16–19	0.25 (0.048, 0.393)	0.21
20–29	1.00 (baseline)	1.00
30–39	1.79 (1.51, 2.03)	1.24
40–49	1.59 (1.25, 1.94)	1.11
50–59	0.13 (0.01, 0.41)	0.00
60–64	0.56 (0.06, 1.54)	0.00
65+	0.42 (0.03, 1.56)	0.00

Exponent of time

The posterior median of the exponent of time, *k*, was 2.42.

Half-life

Increasing the clearance half-life parameter *H* was found to improve model fit in preliminary analysis; however, convergence in the posterior distribution for *H* was unattained after several thousand iterations of the MCMC algorithm, suggesting that there is no finite optimal value of *H*. In light of this, *H* was fixed at 1 000 000 years in the final model, corresponding to virtually no clearance of asbestos from the lungs. However, there was high negative correlation between *H* and *k*; fixing *k* to larger values led to lower simulated samples of *H*. It was thus difficult to obtain a value of *H* that is close to the true value. The large half-life value of 1 000 000 years was selected as it resulted in a better fit than a lower value; however, it should be interpreted with caution.

Diagnostic trend

The inclusion of the diagnostic trend component in the model did not seem to improve the fit of the model. Although the best fitting model was one in which the diagnostic trend component was excluded, this does not necessarily imply that the proportion of missed cases remains unchanged over time; changes may have been encapsulated in the population exposure profile or the background case component of the model.

Age-specific exposure potential

The estimates of the age-specific exposure potential parameters suggested that this was highest among males aged 30 to 49 years, with males aged <15 years and >50 years least likely to be exposed. Convergence of the exposure time profile parameters could not be achieved when all of these were included as estimated parameters.

Exposure profile

Along with the peak exposure year (1963), sharp local peaks in the exposure profile were also present at *Peakyear* -35 and *Peakyear* -15. Attempts were made to smooth the exposure profile before the peak year by changing the assumptions of the population exposure before *Peakyear* -45. However, several attempts resulted in the rate of change in exposure levels at *Peakyear* -45 increasing and failing to converge, as well as the rate at *Peakyear* -35 eventually taking up negative values. In light of this, the rates of change in exposure levels at *Peakyear* -65, *Peakyear* -55 and *Peakyear* -45 were fixed at 0, 1000 and 100 000, respectively. The estimated exposure curve in the final model indicated a high

level of exposure around *Peakyear* -35, soon followed by a sharp decrease in exposure. A rapid increase in population exposure followed from the 1940s to the mid-1960s, reaching a maximum in 1963 and decreasing thereafter.

Background rate

The background rate was estimated at 1.08 cases per million, corresponding to approximately 23 cases in 2006 among males aged 20 to 89 years.

Figure 1A–D shows plots of observed and fitted deaths by year of birth, age of death and year of death for males aged between 20 and 89 years.

Projections

The peak year of mesothelioma mortality among males aged between 20 and 89 years was projected to be 2016 (90% CI: 2015–2017). Although only very few deaths have occurred in males <20 years or >89 years, this estimate has been rescaled to give the total number of deaths among males of all ages. Predicted ratios, projections and credible intervals for mesothelioma mortality in all males are given in Table 3. The estimate of the peak number of deaths in all males is 2038 (90% prediction interval 1929–2156) in the year 2016 (90% CI: 2015–2016). A rapid decline in cases is expected after the peak year. Approximately 91 000 deaths are predicted to occur from 1968 to 2050 with around 61 000 of these occurring from 2007 onwards. Figure 2 shows a plot of fitted and observed deaths by year of death, along with a 90% prediction interval for all male deaths.

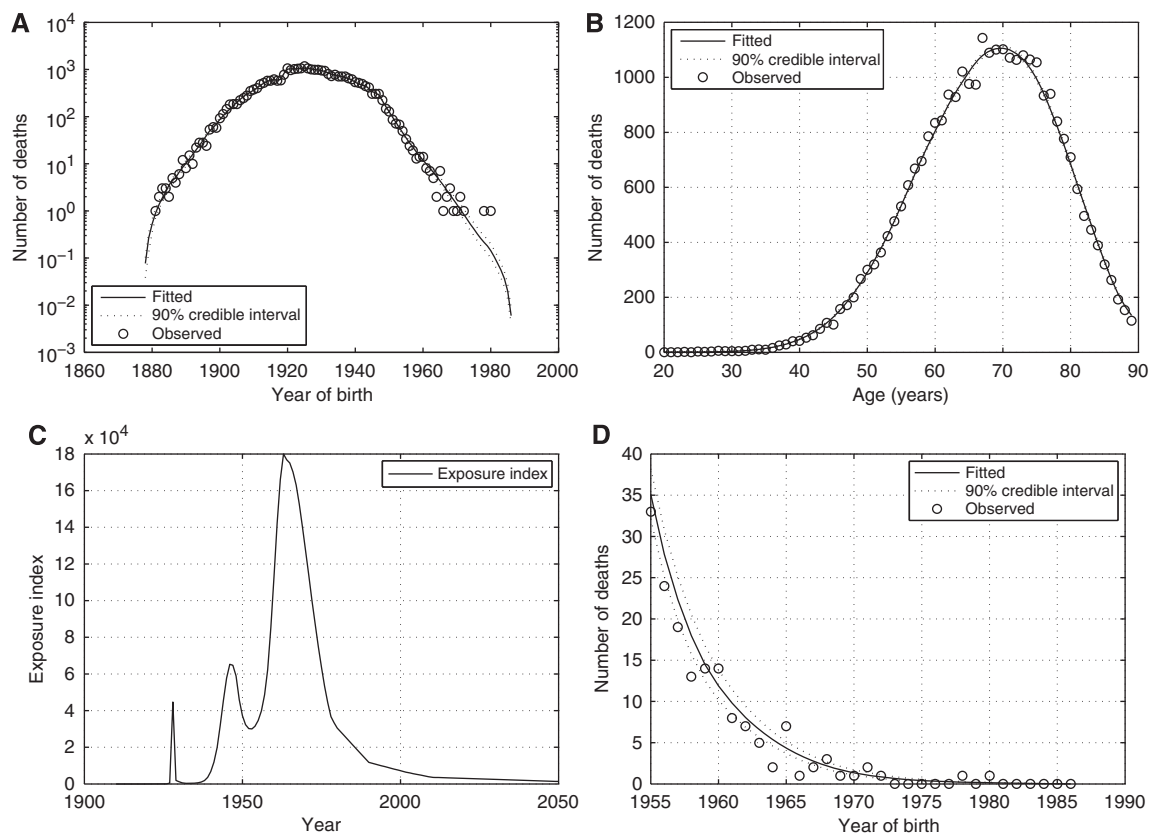


Figure 1 Metropolis–Hastings algorithm. (A) Observed and fitted deaths by year of birth. (B) Observed and fitted deaths by age. (C) Derived exposure index. (D) Observed and fitted deaths for 1955–1985 birth cohorts.

Table 3 Projections of all male mesothelioma deaths

Year	Male 20–89 years Projection (90% prediction interval)
2009	1910 (1827, 1993)
2010	1941 (1855, 2026)
2011	1968 (1870, 2059)
2012	1993 (1897, 2084)
2013	2012 (1913, 2106)
2014	2027 (1926, 2129)
2015	2035 (1929, 2141)
2016	2038 (1928, 2156)
2017	2037 (1928, 2147)
2018	2031 (1912, 2152)
2019	2017 (1903, 2141)
2020	1997 (1871, 2132)
2030	1462 (1314, 1626)
2040	708 (588, 851)
2050	396 (326, 487)

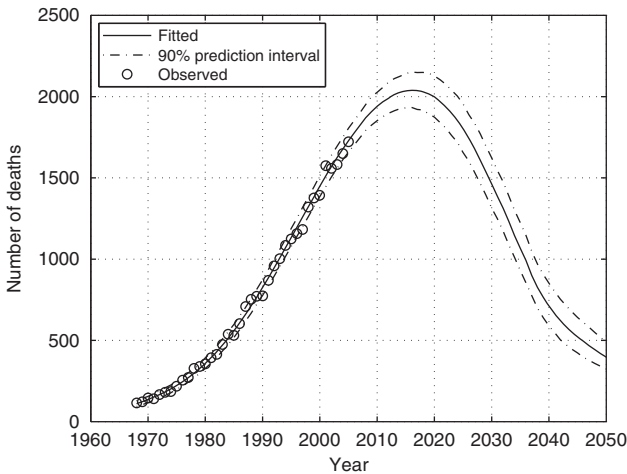


Figure 2 Observed deaths with fitted 50th percentile curve and 90% prediction interval.

Lag period

It has been shown that for many animal tumours, cancer incidence rises approximately as some power of age or time since first exposure to a carcinogen (Doll, 1971). Peto *et al* (1995) fitted a model of this type to mesothelioma mortality data for North American insulation workers and showed that incorporating a lag of 10 years from asbestos exposure to disease occurrence provided a better fit than assuming no lag period (Peto and Selikoff, 1982). A lag of 10 years has subsequently been assumed by several researchers (Hodgson *et al*, 2005) and has also been assumed in this paper. Although there is a significant body of work that supports a lag time of 10 years, a fixed lag does represent a strong assumption. Therefore, a local sensitivity analysis of the lag time was carried out to test the sensitivity of model results to this assumption. Lag times between 0 and 15 years were considered. Results showed that both the peak year and the peak number of deaths were sensitive to the assumed lag. In particular, a lag of 0 resulted in a peak year further into the future, whereas a lag of 15 years moved the peak closer to present time. However, the deviances calculated under these lags indicated a much poorer fit to the data than under a lag of 10 years. The peak year and peak number of deaths were not sensitive to small variations in about a lag of 10 years.

Model adequacy

The deviance residuals may be used to measure the fit of the Poisson model and are defined as

$$r_{A,T}^D = \text{sign}(Y_{A,T} - \hat{\lambda}_{A,T}) \sqrt{2 \left[Y_{A,T} \log \frac{Y_{A,T}}{\hat{\lambda}_{A,T}} - (Y_{A,T} - \hat{\lambda}_{A,T}) \right]} \quad (5)$$

where $r_{A,T}^D$ is the contribution to the deviance of the observation at age A and year T and

$$\text{sign}(x) = \begin{cases} -1 & \text{if } x < 0 \\ 0 & \text{if } x = 0 \\ 1 & \text{if } x > 0 \end{cases}$$

The distribution of the deviance residuals is approximately normal. For a good fit, approximately 95% of the deviance residuals should lie in the range $[-2, 2]$. Out of the 126 deviance residuals resulting from fitting the model, 121 (96%) lie in the range $[-2, 2]$ when using the posterior medians of the Metropolis–Hastings algorithm, suggesting a satisfactory fit.

DISCUSSION

In this analysis we found that a modified version of the model developed by Hodgson *et al* (2005) provided a good statistical fit to mesothelioma data from 1968 to 2006, suggesting that it provides a sound basis for shorter-term projections of future levels of mortality. Updated projections are broadly in agreement with those based on earlier analyses.

The use of an improved optimisation approach based on MCMC and Bayesian techniques provided increased confidence than in previous analyses that the best fitting model was obtained, as well as allowed a more thorough assessment of model adequacy and model parameters to be made. It has also allowed the construction of prediction intervals for the future mortality to be made.

Fitting the model revealed that the profile of estimated population asbestos exposure over time had several local maxima, whereas in previous analyses the profile increased monotonically before the peak year and decreased monotonically thereafter. The estimate of the global peak year of exposure was 1963 with local peaks around 1930 and 1950, after which exposure rapidly decreased. These peaks coincided with specific events that took place in Great Britain that were likely to have had an effect on the use of asbestos, which may explain the observed pattern to some extent, although it seems unlikely that actual changes in population exposure would have been as extreme. The first peak coincides with the Great Depression as well as the establishment of Asbestos Industry Regulations in 1931, which were introduced in Great Britain to regulate the use of asbestos in the asbestos industry, although this sharp peak may have been exaggerated by the assumptions on exposure growth rates in earlier years. Even when these assumptions were relaxed, the pattern of convergence in the parameter estimates representing the exposure growth rates in earlier years still indicated a peak around 1930. This peak, however, only contributes to a small proportion of mesothelioma deaths. When World War II took place between 1939 and 1945, shipbuilding in naval yards increased as the industry saw a large increase in demand. Use of asbestos in naval yards was likely to have increased during that period. After the war, when demand fell, shipbuilding activity decreased and thus the use of asbestos in naval yards was likely to have decreased. The second local peak of asbestos exposure coincides with this post-war reduction in shipyard activity. These features of the population exposure curve persist when refitting the model to observations of mortality to 2001 (the basis for earlier analyses). This suggests that

differences between the updated exposure profile and that of Hodgson *et al* (2005) are because of the improved model-fitting approach rather than because of refinements to the model and additional observations of mortality. As mesothelioma is usually only diagnosed several decades after exposure to asbestos, and as the peak year of mortality has yet to be reached, there is greater uncertainty in the estimated exposure profile from mid-1960s onwards.

In our model, the last year for which the population exposure was estimated was 1978. The extent of the population exposure beyond this point has limited effect on the predicted mesothelioma deaths within the range of years for which observations of mortality are available (up to 2006), and thus on the model fit. Furthermore, predictions of the scale and timing of the peak number of mesothelioma deaths are not highly dependent on exposure after the late 1970s. However, the shape of the exposure curve after 1978 is required to use the model to make longer-term predictions. Some limited investigation of different exposure curves suggested that a levelling off of the exposure in the late 1970s provides a marginally better fit than a continuing very steep decline in exposure. However, such considerations cannot be used as grounds for preferring one exposure curve over another. Decisions regarding the shape of the exposure profile in this region must draw on other sources of evidence about the extent of population exposure more recently.

For our projections we used the same assumptions about exposure beyond the year 2000 as in Hodgson *et al* (2005), and additionally assumed a linear decline in exposure between 1978 and 2000. However, the prediction intervals of our projections incorporate only the uncertainty in the fitted model parameters, and not the unquantifiable but potentially considerable degree of additional uncertainty arising from the particular chosen shape of the exposure curve beyond 1978. For example, if the population exposure levelled off in 1978 and then continued indefinitely at this level rather than continuing to decline, as we have assumed, the model predicts a much slower decline in mortality after the peak year, and consequently much larger estimates of the total mortality to year 2050 that exceed those based on our upper prediction interval.

Although this analysis confirmed that the current model provides a good fit to the observations of mesothelioma mortality to date, and provides a reasonable basis for projections in the short term, it is much less clear whether it provides a good basis for longer-term projections, even if we could be more confident about the exposure curve beyond 1978. Male mortality to date is still dominated by the effect of substantial past occupational exposures, and in these circumstances this model, in which mesothelioma risk depends on a power of time since first exposure, seems to fit the data well.

The estimated number of background cases was 1.08 cases per million population, equivalent to 23 cases in 2006 among males aged 20–89 years. This is in good agreement with the value of 1

to 2% of total cases as suggested by McDonald and McDonald (1996), who carried out backward extrapolation of mesothelioma mortality trends from epidemiological studies from various countries; a figure of 1.15% (95% confidence interval 0.90–1.45) has been suggested by Teta *et al* (2008) for males, based on US mesothelioma patterns between 1973 and 2002. Although the proportion of background cases in recent years among males has been small compared with the relatively large number of asbestos-related cases, the background cases will represent a larger proportion of all cases in future years when the number of asbestos-related cases will decline.

Hodgson *et al* (2005) included a diagnostic trend parameter in their models, which was estimated at 5% in their non-clearance model. The results of our analyses suggested little statistical evidence for a diagnostic trend and no apparent improvement to the fit of the model. Although the best fitting model was one in which the diagnostic trend component was excluded, this does not necessarily imply that the proportion of missed cases has remain unchanged over time; changes in the proportion of missed cases over time may have been encapsulated in the population exposure profile or the background case component of the model.

The peak number of mesothelioma deaths among males aged 20–89 years reported in Hodgson *et al* (2005) was approximately 1846 deaths between 2011 and 2015 based on data up to 2001, which is lower than the peak of 1990 (90% prediction interval 1886–2100) deaths among males ages 20–89 years in the year 2016 predicted in this study. However, more than half of the difference in the peak number of deaths is because of the use of updated projections of the future British population.

Different estimates of peak mesothelioma mortality have been predicted in other countries; in Australia, the peak is expected at approximately 700 cases per year in 2010 (Leigh and Driscoll, 2003). In France, the peak of approximately 2200 cases per year is expected some time after 2020 (Ilg *et al*, 1998), whereas in the Netherlands (Segura *et al*, 2003), up to 900 cases per year of pleural mesothelioma are expected around the year 2028. These projections, among others that have been made for mesothelioma mortality in Europe, indicate that although the number of deaths has been rapidly increasing in recent years, mortality may not reach a peak for several years. Although the pattern of projected future mesothelioma mortality in Britain is broadly consistent with these predictions for other industrialised countries, the scale of mesothelioma mortality varies between countries and rates in Britain are among the highest worldwide (Rake *et al*, 2009). This is a reflection of large-scale importation and use of asbestos particularly in building products. The assumptions that we have made about future exposures are uncertain and the contribution they will make to the cumulative total burden of mesothelioma in the long run will ultimately depend on the effectiveness of current controls to prevent inadvertent exposures because of maintenance activities in buildings that still contain asbestos products.

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EXHIBIT 12

Global mesothelioma deaths reported to the World Health Organization between 1994 and 2008

Vanya Delgermaa,^a Ken Takahashi,^a Eun-Kee Park,^a Giang Vinh Le,^a Toshiyuki Hara^a & Tom Sorahan^b

Objective To carry out a descriptive analysis of mesothelioma deaths reported worldwide between 1994 and 2008.

Methods We extracted data on mesothelioma deaths reported to the World Health Organization mortality database since 1994, when the disease was first recorded. We also sought information from other English-language sources. Crude and age-adjusted mortality rates were calculated and mortality trends were assessed from the annual percentage change in the age-adjusted mortality rate.

Findings In total, 92 253 mesothelioma deaths were reported by 83 countries. Crude and age-adjusted mortality rates were 6.2 and 4.9 per million population, respectively. The age-adjusted mortality rate increased by 5.37% per year and consequently more than doubled during the study period. The mean age at death was 70 years and the male-to-female ratio was 3.6:1. The disease distribution by anatomical site was: pleura, 41.3%; peritoneum, 4.5%; pericardium, 0.3%; and unspecified sites, 43.1%. The geographical distribution of deaths was skewed towards high-income countries: the United States of America reported the highest number, while over 50% of all deaths occurred in Europe. In contrast, less than 12% occurred in middle- and low-income countries. The overall trend in the age-adjusted mortality rate was increasing in Europe and Japan but decreasing in the United States.

Conclusion The number of mesothelioma deaths reported and the number of countries reporting deaths increased during the study period, probably due to better disease recognition and an increase in incidence. The different time trends observed between countries may be an early indication that the disease burden is slowly shifting towards those that have used asbestos more recently.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Malignant mesothelioma is a rare but fatal form of cancer which is difficult to diagnose. The disease is causally linked to asbestos exposure with an etiological fraction of 80% or more.^{1,2} It has been reported that the incidence is much higher in men than women.³ The latency period for mesothelioma after initial exposure to asbestos is typically longer than 30 years and the median survival time after diagnosis is 9–12 months.³ The World Health Organization (WHO) has recognized that asbestos is one of the most important occupational carcinogens and that the burden of asbestos-related disease is rising. Consequently, WHO has declared that asbestos-related diseases should be eliminated throughout the world.⁴

The global mesothelioma burden is unclear. Driscoll et al. estimated that as many as 43 000 people worldwide die from the disease each year.⁵ It has also been estimated that there are around 10 000 mesothelioma cases annually in Australia, Japan, North America and western Europe combined.¹ In addition, Park et al. suggested that one mesothelioma case may be overlooked for every four to five recorded.⁶ Reports of an increase in the incidence of mesothelioma have been published in a wide range of countries.^{7–11} However, to date there is no established global baseline that can be used to evaluate trends in disease occurrence.

Since 1994, data on mesothelioma deaths have been included in the WHO mortality database, which records deaths in WHO Member States in each calendar year. Data are specified by disease category, gender and 5-year age intervals and are integrated across countries using a common format.¹² Data comparability improved with the introduction of the International Classification of Diseases (ICD),¹³ though the category “malignant mesothelioma”

was included only in 1993 with the 10th revision (ICD-10).¹⁴ However, as acknowledged by WHO, accuracy in diagnosing causes of death varies among countries.¹³ By 30 January 2011, mesothelioma death figures were available for a 15-year period. The aim of this study was to improve the understanding and management of malignant mesothelioma by carrying out a descriptive analysis of global data available on deaths caused by the disease.

Methods

We extracted the numbers of mesothelioma deaths recorded in the WHO mortality database as malignant mesothelioma (i.e. ICD-10 category C45 or any subcategory thereof) between 1994 and 2008. In addition, we conducted a literature search of PubMed to identify papers published in English that could provide useful information on national mesothelioma data. However, the data identified lacked detailed information on the numbers of deaths (e.g. on year, age group and gender). Consequently, we used only data from the WHO mortality database in the analysis.

The number of deaths was summed by calendar year and country and was stratified according to demographic characteristics, including gender and anatomical disease site. To calculate mortality rates, national population data were obtained from the WHO health statistics and health information systems¹² and the United States Census Bureau,¹⁵ with priority being given to WHO data.

National counts were further aggregated by region and income level. We merged the smaller regions defined by the United Nations Statistics Division¹⁶ into the five continents: Africa, the Americas, Asia, Europe and Oceania. In addition, we adapted the World Bank categories of national income level¹⁷ to form three categories: low, middle and high income. The World Bank “up-

^a Department of Environmental Epidemiology, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Iseigaoka 1-1, Yahatanishiku, Kitakyushu City, Fukuoka Prefecture 807-8555, Japan.

^b Institute of Occupational and Environmental Medicine, University of Birmingham, Edgbaston, England.

Correspondence to Ken Takahashi (e-mail: ktaka@med.uoeh-u.ac.jp).

(Submitted: 30 January 2011 – Revised version received: 17 May 2011 – Accepted: 17 May 2011 – Published online: 13 June 2011)

per middle" and "lower middle" categories were merged into the middle category.

National data on mesothelioma deaths were available for 1 to 15 years, depending on the country. As a consequence, the number of countries that reported data in any particular year ranged from 3 to 57. This variability was taken into account when calculating the mortality rate for a group of countries by ensuring that any particular country contributed data to both the numerator and denominator of the rate calculation only in those calendar years during which mesothelioma data were available for that country. Age-adjusted mortality rates were calculated using a direct age-adjustment method, with reference to the world population in the year 2000.¹⁸

To assess disease trends over time, we analysed the data from countries that had reported deaths due to mesothelioma for more than 5 years. Regression analysis was used to determine how the age-adjusted mortality rate varied by calendar year. A log-linear trend was assumed and weighting was applied for the size of population at risk each year. To characterize the time trend in the age-adjusted mortality rate, we calculated the annual percentage change in the rate using the slope (i.e. the b value) obtained in the regression model, such that the annual percentage change equalled $100 \times (10^b - 1)$. In addition, 95% confidence intervals (CIs) and P -values were calculated for the annual percentage change.

Data compilation and descriptive statistical analyses were carried out using Microsoft Excel (Microsoft Corporation, Redmond, United States of America). Regression analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, USA). A P -value less than 0.05 was considered indicative of statistical significance.

Results

Table 1 summarizes the study data on all mesothelioma deaths recorded in the WHO mortality database for the period 1994 to 2008. During this time, 92 253 deaths were reported in 83 countries. The crude and age-adjusted mortality rates for all mesothelioma deaths were 6.2 and 4.9 per million population, respectively, and the mean age at death was 70 years. The gender-specific age-adjusted mortality rate for males was 9.0 per million compared with 1.9 per million for females and the male-to-female ratio was 3.6:1.

With regard to anatomical site, the pleura accounted for 41.3% of all mesothelioma deaths and unspecified sites, for 43.1%, far outnumbering the peritoneum and pericardium, which accounted for 4.5% and 0.3% of deaths, respectively. The male-to-female ratio was higher for unspecified sites, the pleura and other sites, at 4.0:1, 3.7:1 and 3.2:1, respectively, compared with 1.8:1 and 1.6:1 for the pericardium and peritoneum, respectively. In fact, mesothelioma of the peritoneum was more than twice as common in females as in males (7.7% versus 3.6%, respectively; data not shown in the table). By anatomical site, the age-adjusted mortality rate was 2.3, 2.3 and 0.3 per million for the pleura, unspecified sites and the peritoneum, respectively. The mean age at death by anatomical site was highest for unspecified sites, at 70.9 years, while it was 70.1 years for patients with pleural mesothelioma and 70.7 years for the category of other sites. Again, findings for these sites contrasted with those for the peritoneum and pericardium, for which the mean age at death was 66.0 and 61.1 years, respectively.

When mesothelioma deaths were analysed by continent, most were found to occur in Europe: almost 50 000 deaths and 54.0% of all deaths worldwide. Moreover, 45% of deaths in Europe were in western regions, while 36% were in northern regions (data not shown in the table). Outside of Europe, mesothelioma deaths occurred most commonly in the Americas and Asia, which accounted for 25.9% and 13.0% of all deaths, respectively. Oceania, which comprised Australia and New Zealand in this study, accounted for 4.6% of all deaths but recorded the highest age-adjusted mortality rate, of 16.0 per million. The second highest was for Europe, at 7.2 per million.

Analysis by national income level showed that 88% and 12% of deaths occurred in high- and middle-income countries, respectively, with almost no deaths recorded in low-income countries. Deaths were concentrated in a relatively small number of countries: 45.2% occurred in either Japan, the United Kingdom of Great Britain and Northern Ireland or the United States of America, while 81.0% occurred in the 10 countries that reported the most deaths. By country, the United Kingdom had the highest age-adjusted mortality rate, at 17.8 per million, followed by Australia, at 16.5 per million, and Italy, at 10.3 per million.

More than three quarters of all deaths were reported after 2000: the correspond-

ing age-adjusted mortality rate was 5.3 per million during 2001 to 2008 compared with 4.0 per million during 1994 to 2000.

Age-specific mesothelioma mortality rates for men and women separately and combined are illustrated by age group in **Fig. 1**. The rate was relatively unchanging at below 10 mesothelioma deaths per million up to 55 years of age, then increased sharply to a peak of 54 per million for individuals aged 75 to 89 years. In men, the rate peaked at 113 per million in the 80–84-year age group; in women, it peaked at 21 per million in the same age group. For pleural mesothelioma, a peak in mortality between the ages of 75 and 89 years was also clearly observed (**Fig. 2**; available at: <http://www.who.int/bulletin/volumes/89/10/11-086678>). For peritoneal mesothelioma, an age peak was noted for individuals aged 65 to 84 years (**Fig. 3**; available at: <http://www.who.int/bulletin/volumes/89/10/11-086678>). Graphs of the age-specific mesothelioma mortality rates for different national income levels demonstrated the same age peak for high-income countries (**Fig. 4**; available at: <http://www.who.int/bulletin/volumes/89/10/11-086678>). The peak was less noticeable for middle-income countries and much less clear for low-income countries. When the age-specific mortality rate was analysed for the two observation periods, the age peak was present for both the 1994 to 2000 period and the 2001 to 2008 period, though the rate was 1.5-fold higher during 2001 to 2008 (**Fig. 5**; available at: <http://www.who.int/bulletin/volumes/89/10/11-086678>).

Forty-six countries reported deaths due to mesothelioma for more than 5 years, with the data covering a total of 85 512 deaths. **Table 2** summarizes the findings of the regression analysis carried out using these data to characterize the time trend in the age-adjusted mortality rate. For the analysis, the data were stratified by gender and other attributes. For all mesothelioma deaths, the age-adjusted mortality rate increased significantly at an annual rate of 5.37%. The annual increase in men, at 5.85%, was more than 60% greater than in women, at 3.48% (**Fig. 6**). When data were analysed by the anatomical site of the mesothelioma, the increasing trend was most apparent for the category of unspecified sites, for which the annual increase was 7.80%. The second most rapid increase was for pleural mesothelioma, at 5.20%, followed by peritoneal mesothelioma, at 2.78% (**Fig. 7**). Analysis of the trend in different continents showed

Table 1. Mesothelioma deaths in the mortality database of the World Health Organization, worldwide, 1994–2008

Characteristic	Deaths		No. of countries reporting deaths	Age at death (years)		AAMR (per million)	M:F ratio
	No.	%		Mean	SD		
Total	92 253	100.0	83	70.0	11.6	4.9	3.6:1
Sex^a							
Male	72 000	78.0	81	69.9	11.2	9.0	NA
Female	20 252	22.0	73	70.2	13.1	1.9	NA
Anatomical disease site^b							
Pleura	38 121	41.3	58	70.1	11.0	2.3	3.7:1
Peritoneum	4 116	4.5	43	66.0	12.6	0.3	1.6:1
Pericardium	298	0.3	30	61.1	15.6	0.03	1.8:1
Other sites	6 184	6.7	53	70.7	12.4	0.4	3.2:1
Unspecified	39 726	43.1	65	70.9	11.5	2.3	4.0:1
Site not reported	3 808	4.1	16	63.6	12.8	2.6	2.6:1
Continent							
Africa	2 333	2.5	4	63.4	12.7	4.8	3.3:1
Americas	23 869	25.9	36	70.5	12.7	3.6	3.3:1
Asia	12 012	13.0	11	69.5	12.2	2.6	3.2:1
Europe	49 779	54.0	30	70.1	10.9	7.2	3.7:1
Oceania	4 260	4.6	2	71.3	10.6	16.0	5.6:1
Country income group^c							
High	81 313	88.1	39	70.9	10.9	6.3	3.9:1
Middle	10 906	11.8	37	63.2	14.0	1.9	1.9:1
Low	22	0.02	2	54.8	16.7	0.4	3.4:1
Not available	12	0.01	5	67.5	11.4	NA ^d	5.0:1
Reporting period							
1994–2000	22 305	24.2	63	68.4	12.5	4.0	3.2:1
2001–2008	69 948	75.8	77	70.5	11.3	5.3	3.7:1
10 countries reporting the highest number of deaths (no. of reporting years)							
United States of America (7)	17 062	18.5	NA	72.8	11.1	5.0	4.2:1
United Kingdom of Great Britain and Northern Ireland (9)	13 517	14.6	NA	71.3	9.9	17.8	5.7:1
Japan (14)	11 212	12.1	NA	70.0	11.9	3.2	3.3:1
Germany (9)	9 569	10.4	NA	70.3	10.6	6.8	3.2:1
France (8)	6 608	7.2	NA	71.8	10.5	7.6	3.4:1
Netherlands (13)	5 141	5.6	NA	70.0	10.2	6.4	4.0:1
Australia (8)	3 747	4.1	NA	71.3	10.7	16.5	5.4:1
Italy (3)	3 706	4.0	NA	71.2	10.6	10.3	2.4:1
South Africa (12)	2 322	2.5	NA	63.4	12.7	6.7	3.3:1
Spain (7)	1 840	2.0	NA	67.8	12.2	3.9	2.9:1

AAMR, age-adjusted mortality rate; M:F, male to female; NA, not applicable; SD, standard deviation.

^a In one case, sex was not specified.

^b Anatomical sites were classified according to the International Classification of Diseases, 10th revision as: C45.0, pleura; C45.1, peritoneum; C45.2, pericardium; C45.7, other sites; C45.9, unspecified.

^c Country income groups were based on adapted World Bank categories of national income level.

^d Population data were not available.

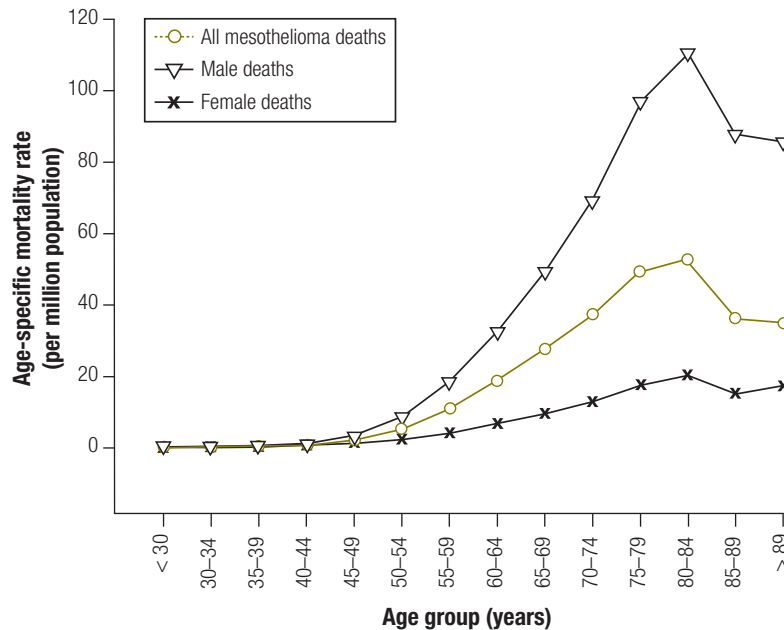
a significant annual increase of 3.67% in Asia and of 3.44% in Europe (Fig. 8; available at: <http://www.who.int/bulletin/volumes/89/10/11-086678>). In addition, there was a significant annual increase of 5.54% in high-income countries, but no significant increase in middle- and low-income countries (Fig. 9). Finally, analysis of data from selected countries identified a significant annual increase of 3.46% in

Japan and a significant annual decrease of 0.84% in the United States (Fig. 10).

Discussion

Our examination of the WHO mortality database through a 15-year window identified over 92 000 deaths from mesothelioma in a total of 83 countries. Although the poor comparability of data from different countries in this database

is well recognized,¹³ we felt that analysing combined mortality data could be justified for several reasons. First, concerns about potential mesothelioma epidemics at a national or regional level are growing and the disease has been targeted for prevention and elimination. Second, because mesothelioma is rare, few international data are available. Third, mortality data may offer an insight into the morbidity

Fig. 1. **Age-specific mesothelioma mortality rate, by age group and gender, worldwide, 1994–2008^a**

^a In total, 71 975 mesothelioma deaths in males and 20 248 deaths in females were reported. The difference between these figures and those recorded in the WHO Mortality Database are due to unavailable data on population, age or sex.

associated with this fatal disease and may aid prevention strategies.

The pattern of mesothelioma we found is inevitably affected by the way countries report data to WHO. The number of countries that submitted underlying cause-of-death data using ICD-10 increased from 4 in 1995, to 75 in 2003, to over 100 in 2007, although about 10 countries continued to use ICD-9.¹³ Three countries reported mesothelioma deaths in 1995, compared with 54 in 2003 and 34 in 2007. The figures for more recent years will probably be revised as data entry continues.

The combined population of the countries reporting data on mesothelioma deaths comprised approximately 29% of the world's population in 2000: 95% of high-income countries, 27% of middle-income countries and 1% of low-income countries. This limited representation is due to the absence of data from populous countries such as China, India and Indonesia.¹⁹ Although the number of countries submitting data is increasing, most deaths reported remain concentrated in a small group of countries: over 80% occurred in the 10 countries that reported the highest

Table 2. **Regression analysis of time trend in age-adjusted^a mesothelioma mortality rate, worldwide, 1994–2008**

Category	Regression parameter ^b			Annual change	
	<i>b</i> or slope	95% CI	<i>P</i>	%	95% CI
Gender					
Male	0.02	0.01 to 0.04	0.0003	5.85	3.25 to 8.51
Female	0.01	0.01 to 0.02	0.0008	3.48	1.74 to 5.26
All	0.02	0.01 to 0.03	0.0002	5.37	3.06 to 7.74
Anatomical disease site					
Pleura	0.02	0.01 to 0.03	0.0006	5.20	2.67 to 7.78
Peritoneum	0.01	0.003 to 0.02	0.0166	2.78	0.59 to 5.03
Unspecified	0.03	0.01 to 0.05	0.0040	7.80	2.90 to 12.93
Continent^c					
Americas	0.03	−0.01 to 0.08	0.1148	7.89	−2.18 to 18.99
Asia	0.02	0.01 to 0.02	<0.0001	3.67	2.64 to 4.71
Europe	0.01	0.003 to 0.03	0.0149	3.44	0.78 to 6.17
Oceania	−0.002	−0.01 to 0.01	0.6295	−0.51	−2.90 to 1.92
Country income group					
High	0.02	0.01 to 0.04	0.0010	5.54	2.66 to 8.50
Middle and low ^d	0.01	−0.001 to 0.02	0.0621	2.16	−0.12 to 4.51
Selected countries					
United States of America	−0.004	−0.01 to −0.001	0.0076	−0.84	−1.34 to −0.34
United Kingdom of Great Britain and Northern Ireland	0.003	−0.004 to 0.01	0.3403	0.68	−0.88 to 2.27
Japan	0.01	0.01 to 0.02	<0.0001	3.46	2.86 to 4.07
South Africa	−0.01	−0.01 to 0.001	0.0959	−1.47	−3.22 to 0.31

CI, confidence interval.

^a Ages were adjusted to the world standard population in 2000.

^b A log-linear regression model was used to analyse the variation in the logarithm of the age-adjusted mortality rate with calendar year. Weighting was applied for each country's population.

^c Africa was excluded because the only country that satisfied the inclusion criteria for the trend analysis was South Africa, which is listed as a selected country.

^d Middle- and low-income countries were combined because only one low-income country satisfied the inclusion criteria for the trend analysis.

number of deaths and over 50% occurred in Europe. By contrast, 26 countries (31%) reported fewer than 10 cumulative mesothelioma deaths each. Data validity may be problematic in these countries. However, underreporting is a common problem with rare diseases that are difficult to diagnose. Without immunohistochemical staining, mesothelioma is often misdiagnosed as lung adenocarcinoma.^{3,20} In this study, we did not include “malignant neoplasm of the pleura” (ICD-9 category 163), although this condition is generally compatible with malignant mesothelioma of the pleura. Hence, our data may underestimate mesothelioma deaths occurring worldwide.

Regression analysis, under the assumption of a log-linear trend, showed that age-adjusted mortality rates increased significantly over time. This suggests that mortality was rising exponentially. The annual change of around 5% we found corresponds to a more than twofold increase in the age-adjusted mortality rate during the 15-year study period. This rise probably reflects both better disease detection and a real increase in incidence.

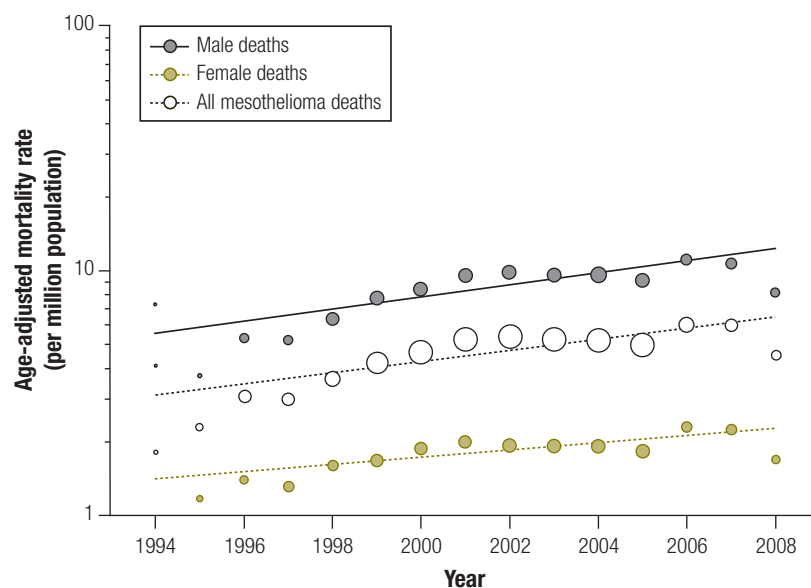
Statistically, the increased mortality rate was influenced by trends in high-income countries, which reported 88% of all mesothelioma deaths. For example, there was a significant decrease in the United States, which ranked first in the number of deaths, a nonsignificant increase in the United Kingdom, which ranked second, and a significant increase in Japan, which ranked third. These trends are consistent with previous reports^{9,21–23} and may reflect the wax and wane of disease with historical asbestos use.²⁴ Accordingly, the burden of disease may be shifting towards countries that used asbestos more recently, such as those in Asia and, to a lesser extent, middle- and low-income countries.

The age-adjusted mortality rate was found to be smaller than the crude mortality rate because mesothelioma deaths were more frequent in developed countries, whose populations are older on average than the reference global population.

The overall mortality rate of less than 10 deaths per million population confirms that the disease is indeed rare. However, the age-specific mortality rate increased steeply with age, to exceed 100 per million in elderly males.

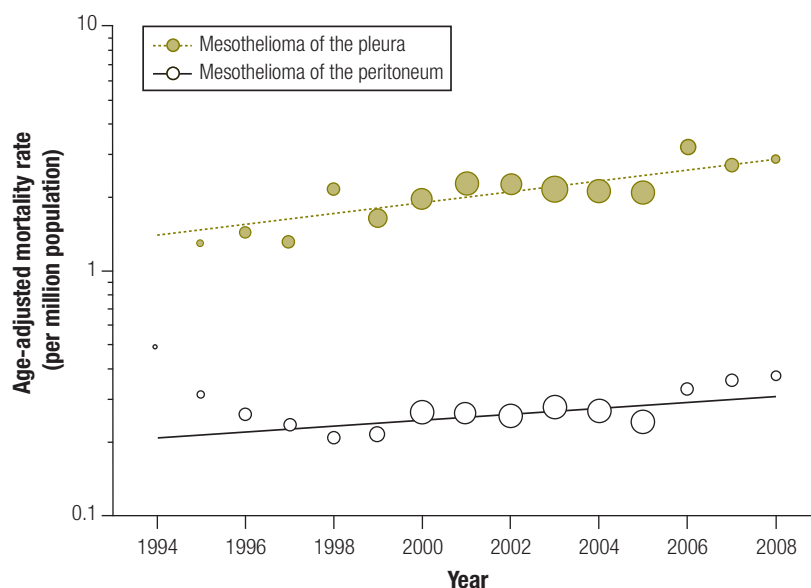
Although the consensus value for the background level of mesothelioma is approximately 1 per million,^{3,25} we previously speculated that this value could be even lower because an analysis of the

Fig. 6. Time trend in age-adjusted mesothelioma mortality rate, by gender, worldwide, 1994–2008



Note: The diameter of each circle is proportional to the size of the population at risk.

Fig. 7. Time trend in age-adjusted mortality rate for pleural and peritoneal mesothelioma, worldwide, 1994–2008



Note: The diameter of each circle is proportional to the size of the population at risk.

ecological relationship between the mortality rate and asbestos use indicated that the graphical intercept was close to zero.²⁶ Consequently, the mortality rates of 1 to 2 per million reported by some middle-income countries may reflect an earlier low but non-zero level of asbestos use.

As previously reported,^{5,27,28} we found that all forms of mesothelioma predominantly affect elderly individuals aged over 70 years. There was almost no difference in age at death between the genders. Some

differences in age at death were observed for different anatomical disease sites: deaths peaked at approximately 70 years for pleural disease, in the middle of the 60–70-year age group for peritoneal disease and at just over 60 years for pericardial disease. For all three anatomical sites, men died 1 to 3 years earlier than women (data not shown). The age at death was lowest in Africa, in middle- and low-income countries and in some specific countries: it was lowest in South Africa. These observations

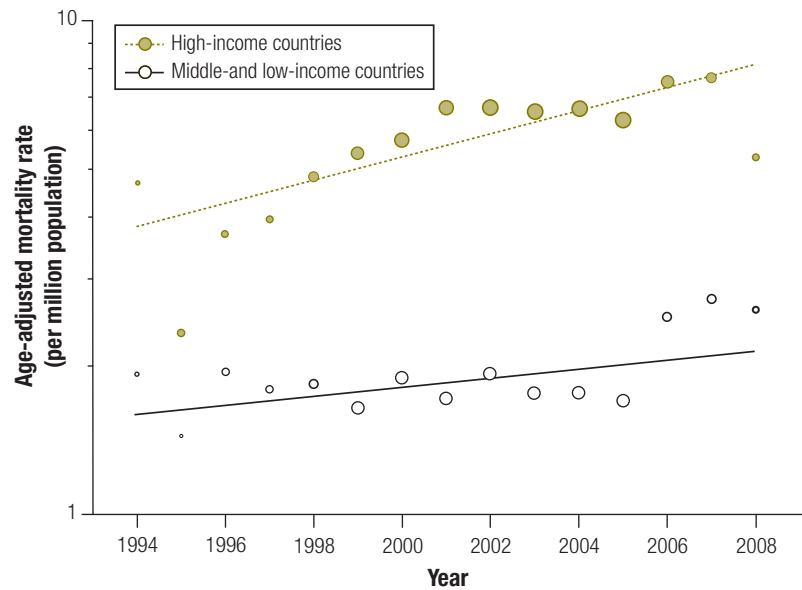
may partially reflect life expectancy in the base populations.

The pleura and unspecified sites were by far the most common disease locations and were reported with similar frequencies. We speculate that, because the gender ratio and the pattern of the age-specific mortality rate were similar for the two, they overlap considerably. The ratio of pleural to peritoneal mesothelioma in this study was 9.2:1. However, a high proportion of unspecified sites was reported by high-incidence countries, such as the United States.^{24,29} If all unspecified sites are assumed in fact to refer to the pleura, then the pleural-to-peritoneal mesothelioma ratio would be more than doubled, at 18.7:1. Therefore, if survival rates for these two types of mesothelioma are similar, the pleural type would appear to be much more prevalent than the peritoneal, contrary to what previous authors have suggested.^{25,30} Furthermore, the male-to-female ratio for peritoneal mesothelioma was much lower than for pleural mesothelioma (1.6:1 versus 3.7:1, respectively) and the age at death was also lower (66.0 years versus 70.1 years, respectively). Consequently, even though the etiological role of asbestos is indisputable, peritoneal mesothelioma may involve unique biological mechanisms that have yet to be elucidated.

Geographically, most mesothelioma deaths occurred in the Americas, primarily the United States, and in Europe, particularly in western and northern regions. Generally, deaths occurred in high-income countries. The 10 nations with the highest cumulative number of deaths belong to the industrialized world and included Japan and South Africa. We recently reported that countries with a high cumulative number of mesothelioma deaths also had high cumulative asbestos use.⁶ South Africa was previously a major producer of asbestos and was the site of the first mesothelioma cluster described.³¹ Mesothelioma mortality varied considerably between regions. For example, the age-adjusted mortality rate was 6-fold higher in Oceania than in Asia, 16-fold higher in high-income countries than in low-income countries and 5.6-fold higher in the United Kingdom than in Japan.

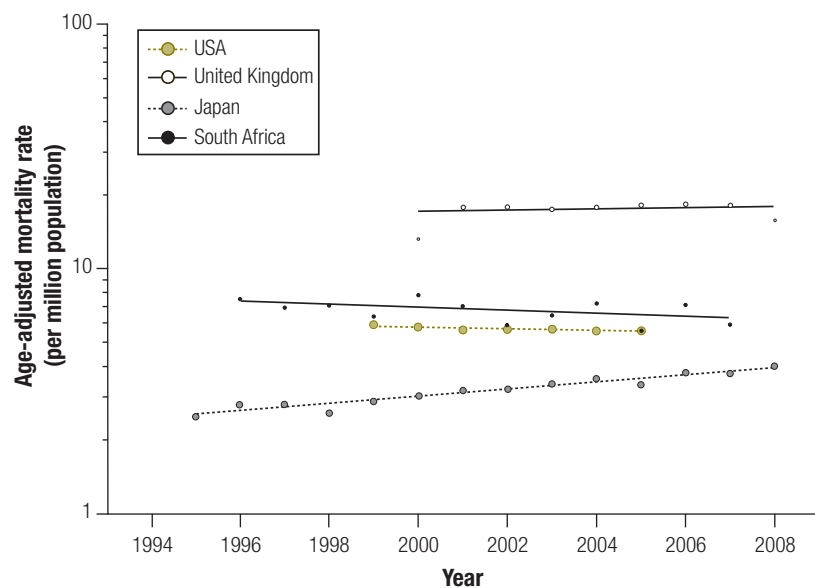
The male-to-female ratio of 3.6:1 we observed was generally in agreement with ratios reported in previous studies.^{2,26,32,33} However, the ratio was very high in the United Kingdom, at 5.7:1, and Australia, at 5.4:1, but very low in middle-income countries, at 1.9:1, and in

Fig. 9. Time trend in age-adjusted mesothelioma mortality rate, by country income,^a worldwide, 1994–2008



^a Data from 23 high-income and 23 middle- and low-income countries were included. Note: The diameter of each circle is proportional to the size of the population at risk.

Fig. 10. Time trend in age-adjusted mesothelioma mortality rate in selected countries, 1994–2008



USA, United States of America.

Note: The diameter of each circle is proportional to the size of the population at risk.

Italy, at 2.4:1. These differences warrant further investigation.

Developing countries are still in the early stages of diagnosing mesothelioma³⁴ and may be prone to misdiagnosis and reporting errors. Along with shorter-life expectancy, these factors may partially account for the higher proportion of disease recorded in younger subjects and the lower peak in age-adjusted mortality rate observed in older populations in middle-

and low-income countries (Table 1 and Fig. 4). It is noteworthy that the age and gender characteristics of those who died from mesothelioma in the earlier part of the observation period, who were mostly in high-income countries, were similar to those currently observed in developing countries. We speculate that developing countries, to the extent that they are spared from asbestos-related disease, may be reporting disease rates close to the

background level. However, since asbestos use has increased more recently in developing than developed countries, developing countries should prepare for an increase in the number of mesothelioma deaths in the coming decades.

The question of the extent to which our data are representative is important for drawing inferences for global health. In a recent study in the United Kingdom, only two thirds of mesothelioma deaths were identified by analysing the underlying cause of death recorded on death certificates.³⁵ We may also have missed a significant proportion of mesothelioma deaths for a similar reason because the WHO data we used came from countries that code the

underlying cause of death using national standards.¹³ Moreover, no data were available for China, India, Kazakhstan, the Russian Federation or Thailand, which have produced or consumed asbestos at substantial levels for many years.⁶

In conclusion, malignant mesothelioma remains a rare form of cancer but the disease is on the rise, probably due to the spread of asbestos use over past decades. Our analysis shows that the disease burden is still predominantly borne by the developed world. However, since asbestos use has recently increased in developing countries, a corresponding shift in disease occurrence is anticipated. Our analysis of the global mortality pattern suggests that

there are early indications of this shift and lends support to the call by international organizations to eliminate asbestos-related diseases and discontinue the use of asbestos throughout the world.^{4,36} ■

Acknowledgements

This work was supported in part by the Asia–Africa Science Platform Programme of the Japan Society for the Promotion of Sciences and the Project for the Development of a Toolkit for the Elimination of Asbestos-Related Diseases commissioned by the Rotterdam Convention Secretariat.

Competing interests: None declared.

ملخص

التبليغ لمنظمة الصحة العالمية عن وفيات ورم المتوسطة بين عامي 1994 و 2008

هي 3.6:1. وتوزع المرض حسب موقع حدوثه التشريحي في: الجنبية 41.3%؛ الصفاق 4.5%؛ التامور 0.3%؛ ومواقع غير محددة 43.1%. وتجانف التوزيع الجغرافي للوفيات نحو البلدان المرتفعة الدخل: وأبلغت الولايات المتحدة الأمريكية عن أعلى عدد، بينما وقعت أكثر من 50% من جميع الوفيات في أوروبا. وبالمقارنة، وقعت أقل من 12% من الوفيات في البلدان المتوسطة والمنخفضة الدخل. وفي المجمل تزايد اتجاه معدل الوفيات المصحح بالعمر في أوروبا واليابان، ولكنه كان يتراجع في الولايات المتحدة. الاستنتاج ازداد عدد وفيات ورم المتوسطة المبلغ عنه وعدد البلدان التي تبلغ عنه أثناء فترة الدراسة، وقد يرجع ذلك إلى تحسن سبل اكتشاف المرض وزيادة معدل وقوعه. وقد يكون التباين في الاتجاهات الزمنية الملاحظة بين البلدان إشارة مبكرة على أن عبء المرض ينتقل ببطء نحو البلدان الأكثر حداثة في استخدام الأسبست.

الغرض إجراء تحليل وصفي لوفيات ورم المتوسطة المبلغ عنها على الصعيد العالمي بين عامي 1994 و 2008. الطريقة استخلص الباحثون معطيات وفيات ورم المتوسطة المبلغ عنها من قاعدة معطيات الوفيات التابعة لمنظمة الصحة العالمية منذ عام 1994، حين بدأ تسجيل المرض لأول مرة. كما سعى الباحثون وراء المعلومات الموجودة في المصادر المكتوبة باللغة الإنكليزية. وحسبت معدلات الوفيات الخام والمعدلات المصححة بالعمر، وجرى تقييم لاتجاهات الوفيات عن طريق التغير في النسبة المئوية السنوية لمعدل الوفيات المصحح بالعمر. النتائج لقد أبلغ عن وقوع 92253 وفاة من قبل 83 بلداً. وكان معدل الوفيات الخام 6.2 ومعدل الوفيات المصحح بالعمر 4.9 وفاة لكل مليون شخص من السكان. ازداد سنوياً معدل الوفيات المصحح بالعمر بمقدار 5.37%، ونتيجة لذلك ازداد إلى أكثر من الضعف في غضون فترة الدراسة. وكان متوسط العمر وقت الوفاة هو 70 عاماً، وكانت نسبة الذكور إلى الإناث

摘要

1994-2008年间向世界卫生组织报告的全球间皮瘤死亡人数

目的 旨在对1994-2008年间全球范围内报告的间皮瘤死亡人数进行描述性分析。

方法 我们提取了自1994年该疾病首次记录以来向世界卫生组织死亡数据库报告的间皮瘤死亡数据。我们还从其他的英语语言来源检索了相关信息。同时对粗死亡率和年龄调整死亡率进行计算，并从年龄调整死亡率的年度百分比变化评估死亡率趋势。

结果 总共有83个国家报告了92 253例间皮瘤死亡。粗死亡率和年龄调整死亡率分别为每百万人群6.2例和4.9例。年龄调整死亡率每年增加5.37%，而在整个研究期间则翻了一番。死亡的平均年龄是70岁，男女比例为3.6:1。从

解剖部位看，疾病的分布为：胸膜，41.3%；腹膜，4.5%；心包，0.3%；非指定部位，43.1%。死亡的地理分布向高收入国家偏移：美国报告的死亡人数最多，而超过50%的死亡率发生在欧洲。相比之下，仅有低于12%的死亡发生在中低收入国家。年龄调整死亡率在欧洲和日本总体呈上升趋势，而在美国整体呈下降趋势。

结论 研究期间所报告的间皮瘤死亡人数和报告死亡人数的国家数量均有所增加，可能由于有更好的疾病识别能力，同时该病的发病率也再增加。所观察到的国家间的不同时间趋势可能表明疾病负担正在慢慢向那些近来使用石棉的国家转移的一个早期迹象。

Résumé

Les décès mondiaux par mésothéliome rapportés à l'Organisation mondiale de la Santé entre 1994 et 2008

Objectif Réaliser une analyse descriptive des décès par mésothéliome, rapportés à l'échelle mondiale entre 1994 et 2008.

Méthodes Nous avons extrait les données sur les décès par mésothéliome rapportés à la base de données de mortalité de l'Organisation mondiale

de la Santé depuis 1994, lorsque la maladie a été enregistrée pour la première fois. Nous avons également cherché des informations à partir d'autres sources en langue anglaise. Les taux de mortalité brut et ajusté selon l'âge ont été calculés, et les tendances de la mortalité ont été

évaluées à partir de la modification du pourcentage annuel du taux de mortalité ajusté selon l'âge.

Résultats Au total, 92 253 décès par mésothéliome ont été signalés par 83 pays. Les taux de mortalité brut et ajusté selon l'âge étaient de 6,2 et 4,9 par million d'habitants, respectivement. Le taux de mortalité ajusté selon l'âge a augmenté de 5,37% par an et a, par conséquent, plus que doublé au cours de la période d'étude. L'âge moyen au décès était de 70 ans et le ratio hommes-femmes était de 3,6:1. La distribution de la maladie selon le site anatomique était la suivante: plèvre, 41,3%; péritoine, 4,5%; péricarde, 0,3%, et sites non précisés, 43,1%. La répartition géographique des décès était biaisée vers les pays à revenus élevés: les États-Unis d'Amérique en ont signalé le plus grand nombre, tandis que

plus de 50% de tous les décès sont survenus en Europe. En revanche, moins de 12% des décès sont survenus dans les pays à revenus faible et moyen. La tendance générale du taux de mortalité ajusté selon l'âge était en augmentation en Europe et au Japon, mais en baisse aux États-Unis.

Conclusion Le nombre de décès par mésothéliome rapportés et le nombre de pays rapportant des décès ont augmenté au cours de la période d'étude, probablement en raison d'une meilleure identification de la maladie et d'une augmentation de l'incidence. Les différentes tendances au cours du temps observées entre les pays peuvent être une indication précoce du fait que la charge de morbidité se déplace lentement vers les personnes qui ont plus récemment utilisé l'amiante.

Резюме

Число случаев смерти от мезотелиомы в мире, зафиксированных Всемирной организацией здравоохранения в 1994–2008 гг.

Цель Провести описательный анализ случаев смерти от мезотелиомы в мире, зафиксированных в 1994–2008 гг.

Методы Мы выделили данные по случаям смерти от мезотелиомы, зафиксированным в базе данных ВОЗ о смертности, начиная с 1994 года, когда сведения по данному заболеванию начали впервые учитываться в базе данных. Мы также провели поиск информации по другим англоязычным источникам. Рассчитывались общий и стандартизированный по возрасту коэффициенты смертности. Тенденции в изменении смертности оценивались как годовое процентное изменение в стандартизированной по возрасту смертности.

Результаты Всего было зарегистрировано 92 253 случая смерти от мезотелиомы в 83 странах. Общий коэффициент и стандартизированная по возрасту смертность составили 6,2 и 4,9 случаев на один миллион населения соответственно. Стандартизированная по возрасту смертность растет на 5,37% в год, и в результате более чем удвоилась за изучаемый период времени. Средний возраст на момент смерти составлял 70 лет, и отношение показателя мужчин к показателю женщин было 3,6:1. Распределение

заболевания по анатомической локализации: плевра – 41,3%, брюшная полость – 4,5%, перикард – 0,3%, неуточненная локализация – 43,1%. Географическое распределение случаев смерти смещалось в сторону стран с высоким доходом: о наибольшем числе смертей сообщили Соединенные Штаты Америки, в то время как 50% всех случаев смерти отмечено в Европе. Напротив, менее чем 12% случаев смерти произошли в странах со средним и низким доходом. Общая тенденция стандартизированного по возрасту коэффициента смертности увеличивалась в Европе и Японии, но уменьшалась в США.

Вывод Количество сообщений о случаях смерти от мезотелиомы и число стран, предоставивших данные о смертности, за изучаемый период увеличились, вероятно, вследствие лучшего распознавания заболевания и увеличения заболеваемости. Различия во временных тенденциях, наблюдаемых в разных странах, могут быть опережающим индикатором смещения бремени заболеваемости в страны, вплоть до недавнего времени использовавшие асбест.

Resumen

Muertes por mesotelioma en todo el mundo notificadas a la Organización Mundial de la Salud entre 1994 y 2008

Objetivo Llevar a cabo un análisis descriptivo de las muertes por mesotelioma notificadas en todo el mundo entre los años 1994 y 2008.

Métodos Hemos recopilado datos sobre muertes por mesotelioma notificadas a la base de datos de mortalidad de la Organización Mundial de la Salud desde 1994, cuando se registró por primera vez la enfermedad. También hemos obtenido información de otras fuentes de lengua inglesa. Se calcularon las tasas de mortalidad bruta y de mortalidad ajustada en función de la edad, y se evaluaron las tendencias de mortalidad a partir del cambio en el porcentaje anual de la tasa de mortalidad ajustada en función de la edad.

Resultados En total, se notificaron 92 253 muertes por mesotelioma en 83 países. Las tasas de mortalidad bruta y de mortalidad ajustada en función de la edad fueron de 6,2 y 4,9 por millón de habitantes, respectivamente. La tasa anual de mortalidad ajustada en función de la edad aumentó en un 5,37% y, en consecuencia, se duplicó durante el periodo de estudio. La edad media en el momento del fallecimiento fue de 70 años y la proporción hombre-mujer fue de 3,6:1. La distribución

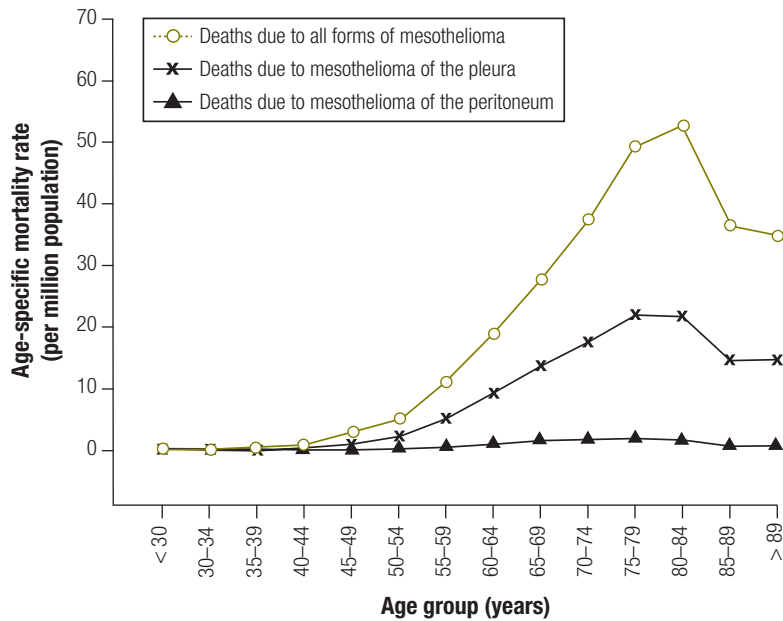
de la enfermedad por regiones anatómicas fue: pleura, 41,3%; peritoneo, 4,5%; pericardio, 0,3%; y lugares no especificados, 43,1%. La distribución geográfica de las muertes mostró una mayor tendencia en los países de renta alta: los Estados Unidos de América registraron el número más elevado, mientras que más del 50% de todas las muertes se produjeron en Europa. Por el contrario, menos de un 12% de las muertes se produjeron en países de renta media o baja. La tendencia generalizada en la tasa de mortalidad ajustada en función de la edad fue aumentando en Europa y Japón, mientras que en los Estados Unidos fue descendiendo.

Conclusión Durante el periodo de estudio, se observó un aumento en el número de muertes notificadas por mesotelioma y en el número de países que notificaron muertes por mesotelioma. Probablemente, esto se debe a una mejora en el reconocimiento de la enfermedad y a un aumento de su incidencia. Las diferentes tendencias entre países observadas en el tiempo, se pueden convertir en un indicador temprano de que la carga de la enfermedad está cambiando lentamente hacia aquellos países que han utilizado amianto más recientemente.

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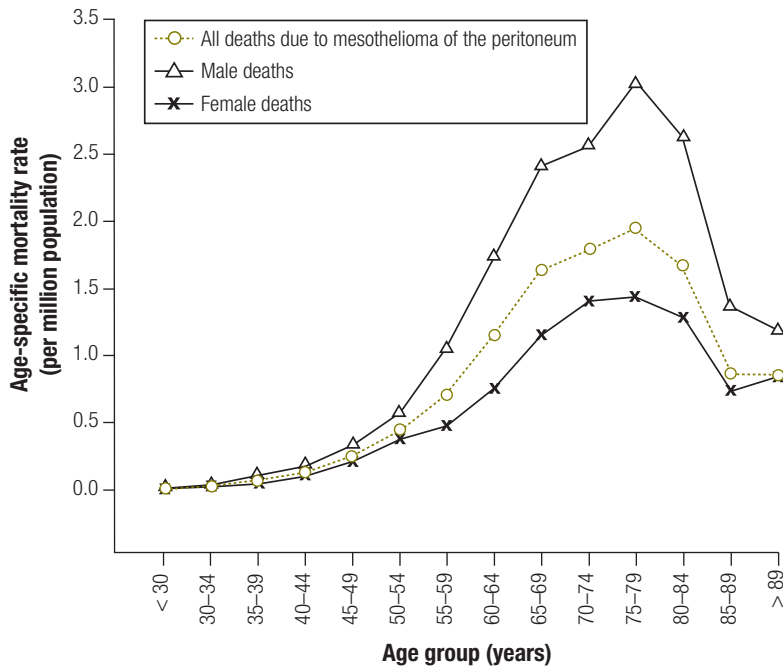
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Fig. 2. **Age-specific mesothelioma mortality rate, by age group and disease site, worldwide, 1994–2008^a**



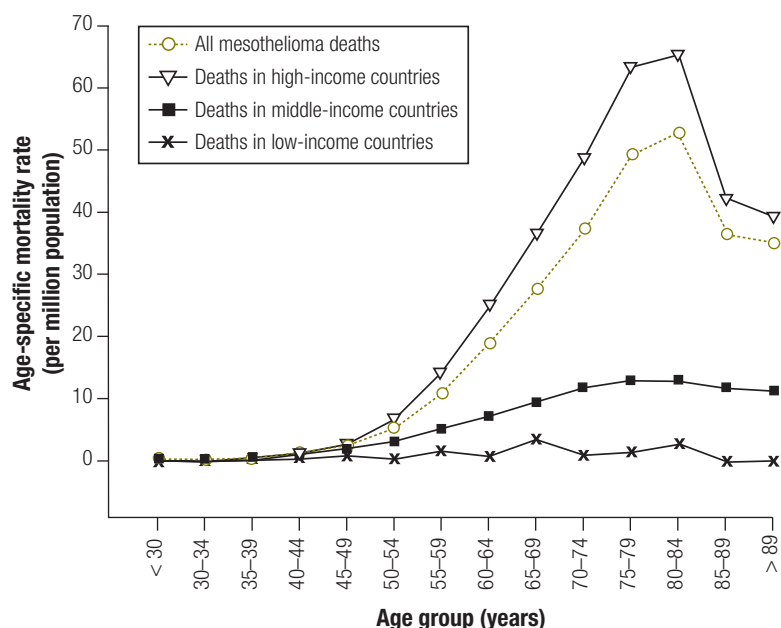
^a Of a total of 92 224 mesothelioma deaths, 38 111 were due to mesothelioma of the pleura and 4116 were due to mesothelioma of the peritoneum. The difference between these figures and those recorded in the WHO Mortality Database are due to unavailable data on population or age.

Fig. 3. **Age-specific peritoneal mesothelioma mortality rate, by age group and gender, worldwide, 1994–2008^a**



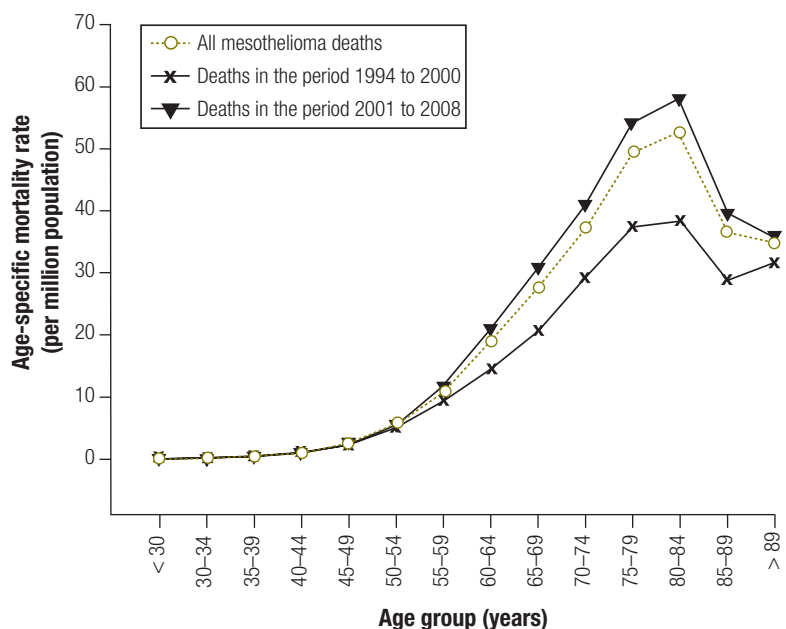
^a Of the 4116 deaths due to mesothelioma of the peritoneum, 2556 occurred in males and 1560 in females.

Fig. 4. **Age-specific mesothelioma mortality rate, by age group and country income, worldwide 1994–2008^a**



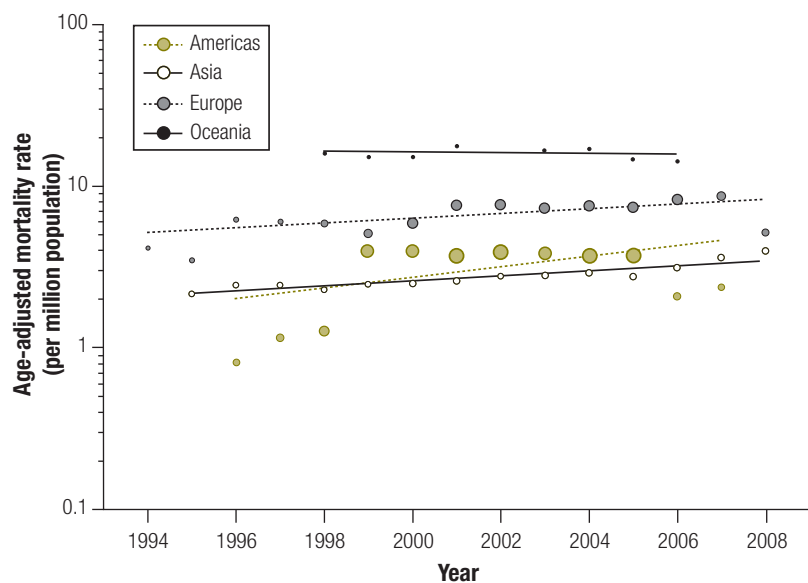
^a Of the 92 224 mesothelioma deaths reported by 83 countries, 81 304 were reported by 39 high-income countries, 10 897 were reported by 37 middle-income countries and 22 were reported by two low-income countries. The difference between these figures and those recorded in the WHO Mortality Database are due to unavailable data on population or age.

Fig. 5. **Age-specific mesothelioma mortality rate, by age group and reporting period, worldwide, 1994–2008^a**



^a Of 92 224 mesothelioma deaths, 22 291 occurred between 1994 and 2000, while 69 933 occurred between 2001 and 2008. The difference between these figures and those recorded in the WHO Mortality Database are due to unavailable data on population or age.

Fig. 8. Time trend in age-adjusted mesothelioma mortality rate in selected continents,^a 1994–2008^b



^a Africa was excluded because the only country that satisfied the inclusion criteria for the trend analysis was South Africa, which is reported in Fig. 10.

Note: The diameter of each circle is proportional to the size of the population at risk.

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EXHIBIT 13

Talc and Asbestos – J&J

David Madigan, PhD

1. Credentials

1. I am Provost and Senior Vice-President for Academic Affairs at Northeastern University in Boston where I am also Professor of Statistics in the Khoury College of Computer Sciences. From 2007 to 2020 I was Professor of Statistics at Columbia University in New York City. From 2013 to 2018 I was also the Executive Vice-President of Arts and Sciences and Dean of the Faculty at Columbia and, from 2008 to 2013 I was chair of the Columbia Department of Statistics. I received my bachelor's degree in Mathematical Sciences from Trinity College Dublin in 1984 and was awarded the College's gold medal. In 1990, I received a Ph.D. in Statistics, also from Trinity College. I have worked in the past for KPMG, SkillSoft, University of Washington, AT&T Labs, and Soliloquy Inc. From 2005 to 2007 I was Professor of Statistics and Dean of Physical and Mathematical Sciences at Rutgers University. Prior to serving as Dean I was Director of the Rutgers University Institute of Biostatistics. I am an elected Fellow of both the Institute of Mathematical Statistics and the American Statistical Association, as well as the American Association for the Advancement of Science, and was the 36th most cited mathematician worldwide from 1995-2005. I was an Institute of Mathematical Statistics Medallion Lecturer in 2009. I served a term as the Editor of *Statistical Science* from 2008 to 2010, the highest impact journal in Statistics.
2. I have published more than 200 technical papers on Bayesian statistics, biostatistics, pharmacovigilance, statistical graphics, Monte Carlo methods, computer-assisted learning, information retrieval, and text mining. Within the last few years I have consulted for Bayer, Heron Therapeutics, Jarvik Heart, Lilly, Pfizer, and Shire on a variety of issues, many related to drug safety. I have considerable statistical experience with clinical trials including the design and analysis of pain studies at the University of Washington and the Fred Hutchinson Cancer Research Center, both in Seattle, and service as a statistical consultant to multiple internal and external clients, particularly while I was director of the Institute of Biostatistics at Rutgers University, and continuing with Bayer and Shire Plc.
3. Drug safety is one of my significant research interests, with a focus on the development and application of statistical methods for pharmacovigilance. I have published my work in Drug Safety, Pharmacoepidemiology and Drug Safety, Therapeutic Advances in Drug Safety, Epidemiology, the American Journal of Epidemiology, and other journals. I have also served as an investigator in the Mini-Sentinel project. Mini-Sentinel is a pilot project sponsored by the FDA to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. In 2010-11, I led the Mini-Sentinel Working Group on case-based methods in active surveillance. In addition, from 2010 to 2013 I was a Principal Investigator for the Observational Medical Outcomes Partnership (OMOP), a public-private partnership between the FDA and the pharmaceutical industry. The partnership conducted a multi-year initiative to research methods that are feasible and

useful to analyze existing healthcare databases to identify and evaluate safety and benefit issues of drugs already on the market. The OMOP work now continues in the Observational Health Data Sciences and Informatics (OHDSI) collaborative where I co-direct the Columbia-based coordinating center. I was a member of the FDA's Drug Safety and Risk Management Advisory Committee (DSaRM) from 2011 to 2014 and served the FDA as a consultant from 2014 to 2017. DSaRM advises the FDA Commissioner on risk management, risk communication, and quantitative evaluation of spontaneous reports for drugs for human use and for any other product for which the FDA has regulatory responsibility. From 2010 to 2011 I was a member of a sub-committee of the FDA Science Board charged with reviewing the Center for Drug Evaluation and Research's pharmacovigilance program.

4. Further information concerning my background, training, and experience, including a complete list of my publications, is reflected in my curriculum vitae, a copy of which is attached as Appendix 2. A list of the testimony I have provided in the last four years is attached as Appendix 3.

2. Research Questions

5. I was asked to address the following questions:
 - Could the 90 Johnson & Johnson talcum powder containers (out of 129) in which MAS detected asbestos be the only 90 with asbestos?
 - Could the 70 Johnson's talcum Baby Powder containers (out of 104) in which MAS detected asbestos be the only 70 with asbestos?
 - What is the probability that a particular plaintiff was exposed to asbestos?
 - How many containers with asbestos was that plaintiff exposed to?
 - Repeat the previous two calculations by talc source.
6. I provide the results of my calculations as Opinions 1, 2, and 3 below. I also provide equivalent calculations drawing solely on MAS's U.S. samples (107 containers total; Opinions 4, 5, and 6), MAS's J&J Archive U.S. samples (50 containers total; Opinions 7, 8, and 9) and MAS's "outside J&J Archive" U.S. samples (57 containers total; Opinions 10, 11, and 12). I provide my source-specific analyses as Opinion 13. MAS provided the requisite testing data for these calculations on January 31st, 2021.
7. Note that I have updated my calculations a number of times in the past as MAS has produced incremental test results. Over this period, my conclusions have not changed. Furthermore, I do not expect them to change meaningfully if MAS conducts further testing.
8. I was asked to provide an assessment of studies by Rubino *et al.*, Coggiola *et al.*, Pira *et al.*, and Selevan *et al.* I was asked to calculate the statistical power of the Rubino *et al.* study with respect to mesothelioma. I was also asked to comment on epidemiology in general and observational study design. Appendix A provides the R code for the various calculations.
9. I was asked to calculate the statistical power of three talc pleurodesis studies with

respect to mesothelioma.

10. The approach I have taken to the work would have been the same had Johnson & Johnson hired me to carry out the analyses. I am being compensated at the rate of \$700 per hour for my work on this matter. As I continue to review the data (or review newly provided data) I reserve the right to supplement and refine my report. All the opinions I express herein I hold to a reasonable degree of scientific certainty.

3. Opinions

Opinion 1.

11. These essentially could not be the only 90 containers of Johnson & Johnson talcum powder that contain asbestos.
12. Suppose n Johnson & Johnson talcum powder containers were ever produced. What is the probability that a sample of 129 would find the only 90 that exist?

n	Probability of finding the only 90
100	n/a
1,000	1.5×10^{-97}
10,000	3.6×10^{-189}
100,000	2.5×10^{-279}
1,000,000	$< 2.2 \times 10^{-308}$
10,000,000	$< 2.2 \times 10^{-308}$
100,000,000	$< 2.2 \times 10^{-308}$
1,000,000,000	$< 2.2 \times 10^{-308}$

13. These essentially could not be the only 70 Johnson & Johnson Baby Powder containers that contain asbestos.
14. Suppose n Johnson's talcum Baby Powder containers were ever produced. What is the probability that a sample of 104 would find the only 70 that exist?

n	Probability of finding the only 70
100	n/a
1,000	4.1×10^{-82}
10,000	4.4×10^{-153}
100,000	3.6×10^{-223}
1,000,000	3.5×10^{-293}
10,000,000	$< 2.2 \times 10^{-308}$
100,000,000	$< 2.2 \times 10^{-308}$
1,000,000,000	$< 2.2 \times 10^{-308}$

15. For comparison purposes, the probability of winning the Powerball Lottery is 3.4×10^{-9} .

Opinion 2.

16. Suppose a plaintiff used n Johnson & Johnson talcum powder containers. What is the probability that this plaintiff was *never* exposed to asbestos?

n	Probability plaintiff was not exposed
10	1.5×10^{-5}
20	8.9×10^{-9}
30	1.4×10^{-12}
50	3.6×10^{-18}
75	4.7×10^{-25}
100	7.0×10^{-30}
200	4.8×10^{-46}
300	6.9×10^{-56}
400	5.8×10^{-65}
500	2.6×10^{-71}

17. Suppose a plaintiff used n Johnson & Johnson Baby Powder containers. What is the probability that a plaintiff was *never* exposed to asbestos?

n	Probability plaintiff was not exposed
10	3.6×10^{-5}
20	5.3×10^{-9}
30	2.2×10^{-12}
50	3.7×10^{-18}
75	4.5×10^{-24}
100	5.2×10^{-29}
200	3.1×10^{-43}
300	7.2×10^{-53}
400	3.6×10^{-60}
500	4.8×10^{-66}

Opinion 3.

18. Depending on each plaintiff's usage of Johnson & Johnson talcum powder containers, the number of asbestos-containing containers each plaintiff was exposed to is as follows:

Number of Containers Used	95% Prediction Interval for Number of Asbestos-containing containers
10	(3 , 10)
20	(8 , 18)

30	(14 , 26)
50	(26 , 42)
75	(41 , 62)
100	(56 , 81)
200	(116 , 159)
300	(177 , 237)
400	(238 , 315)
500	(299 , 392)

19. Depending on each plaintiff's usage of Johnson & Johnson Baby Powder containers, the number of asbestos-containing containers each plaintiff was exposed to is as follows:

Number of Containers Used	95% Prediction Interval for Number of Asbestos-containing containers
10	(3 , 9)
20	(8 , 18)
30	(13 , 26)
50	(24 , 41)
75	(38 , 61)
100	(52 , 80)
200	(109 , 156)
300	(167 , 233)
400	(224 , 309)
500	(281 , 385)

20. These 95% intervals are constructed so that 95% of such intervals contain the corresponding true value. Thus, for example, if a plaintiff used 20 containers, the number of those containers with asbestos is between 8 and 18 with 95% "confidence."

Opinion 4 (U.S. Containers).

21. These essentially could not be the only 74 containers of Johnson & Johnson talcum powder that contain asbestos.
22. Suppose n Johnson & Johnson talcum powder containers were ever produced. What is the probability that a sample of 107 would find the only 74 that exist?

n	Probability of finding the only 74
100	n/a
1,000	2.3×10^{-86}
10,000	1.9×10^{-161}
100,000	1.5×10^{-235}
1,000,000	1.4×10^{-309}

10,000,000	$< 2.2 \times 10^{-308}$
100,000,000	$< 2.2 \times 10^{-308}$
1,000,000,000	$< 2.2 \times 10^{-308}$

23. These essentially could not be the only 55 Johnson & Johnson Baby Powder containers that contain asbestos.
24. Suppose n Johnson's talcum Baby Powder containers were ever produced. What is the probability that a sample of 83 would find the only 55 that exist?

n	Probability of finding the only 55
100	1.7×10^{-7}
1,000	5.9×10^{-70}
10,000	1.5×10^{-125}
100,000	1.3×10^{-180}
1,000,000	1.3×10^{-235}
10,000,000	1.3×10^{-290}
100,000,000	$< 2.2 \times 10^{-308}$
1,000,000,000	$< 2.2 \times 10^{-308}$

25. For comparison purposes, the probability of winning the Powerball Lottery is 3.4×10^{-9} .

Opinion 5 (U.S. Containers).

26. Suppose a plaintiff used n Johnson & Johnson talcum powder containers. What is the probability that this plaintiff was *never* exposed to asbestos?

n	Probability plaintiff was not exposed
10	2.1×10^{-5}
20	2.0×10^{-9}
30	5.6×10^{-13}
50	4.8×10^{-19}
75	2.8×10^{-25}
100	1.8×10^{-30}
200	1.9×10^{-45}
300	1.3×10^{-55}
400	2.3×10^{-63}
500	1.6×10^{-69}

27. Suppose a plaintiff used n Johnson & Johnson Baby Powder containers. What is the probability that a plaintiff was *never* exposed to asbestos?

<i>n</i>	Probability plaintiff was not exposed
10	5.9×10^{-5}
20	1.6×10^{-8}
30	1.4×10^{-11}
50	9.9×10^{-17}
75	6.9×10^{-22}
100	4.1×10^{-26}
200	5.1×10^{-38}
300	6.4×10^{-46}
400	7.6×10^{-52}
500	1.4×10^{-56}

Opinion 6 (U.S. Containers).

28. Depending on each plaintiff's usage of Johnson & Johnson talcum powder containers, the number of asbestos-containing containers each plaintiff was exposed to is as follows:

Number of Containers Used	95% Prediction Interval for Number of Asbestos-containing containers
10	(3 , 10)
20	(8 , 18)
30	(14 , 26)
50	(25 , 42)
75	(40 , 62)
100	(54 , 81)
200	(114 , 159)
300	(173 , 237)
400	(232 , 315)
500	(292 , 393)

29. Depending on each plaintiff's usage of Johnson & Johnson Baby Powder containers, the number of asbestos-containing containers each plaintiff was exposed to is as follows:

Number of Containers Used	95% Prediction Interval for Number of Asbestos-containing containers
10	(2 , 9)
20	(7 , 18)
30	(13 , 26)
50	(23 , 41)
75	(37 , 60)
100	(50 , 80)
200	(105 , 156)

300	(160 , 233)
400	(215 , 309)
500	(270 , 385)

30. These 95% intervals are constructed so that 95% of such intervals contain the corresponding true value. Thus, for example, if a plaintiff used 20 containers, the number of those containers with asbestos is between 8 and 18 with 95% “confidence.”

Opinion 7 (J&J Archive U.S. Containers).

31. These essentially could not be the only 36 containers of Johnson & Johnson talcum powder that contain asbestos.
32. Suppose n Johnson & Johnson talcum powder containers were ever produced. What is the probability that a sample of 50 would find the only 36 that exist?

n	Probability of finding the only 36
100	4.7×10^{-16}
1,000	6.6×10^{-55}
10,000	3.7×10^{-91}
100,000	3.5×10^{-127}
1,000,000	3.5×10^{-163}
10,000,000	3.5×10^{-199}
100,000,000	3.5×10^{-235}
1,000,000,000	3.5×10^{-271}

33. These essentially could not be the only 18 Johnson & Johnson Baby Powder containers that contain asbestos.
34. Suppose n Johnson’s talcum Baby Powder containers were ever produced. What is the probability that a sample of 27 would find the only 18 that exist?

n	Probability of finding the only 18
100	1.5×10^{-13}
1,000	3.5×10^{-32}
10,000	3.0×10^{-50}
100,000	3.0×10^{-68}
1,000,000	3.0×10^{-86}
10,000,000	3.0×10^{-104}
100,000,000	3.0×10^{-122}
1,000,000,000	3.0×10^{-140}

35. For comparison purposes, the probability of winning the Powerball Lottery is 3.4×10^{-9} .

Opinion 8 (J&J Archive U.S. Containers).

36. Suppose a plaintiff used n Johnson & Johnson talcum powder containers. What is the probability that this plaintiff was *never* exposed to asbestos?

n	Probability plaintiff was not exposed
10	2.6×10^{-5}
20	8.6×10^{-9}
30	1.3×10^{-11}
50	4.7×10^{-16}
75	3.1×10^{-20}
100	1.6×10^{-23}
200	2.3×10^{-32}
300	5.8×10^{-38}
400	4.5×10^{-42}
500	2.5×10^{-45}

37. Suppose a plaintiff used n Johnson & Johnson Baby Powder containers. What is the probability that this plaintiff was *never* exposed to asbestos?

n	Probability plaintiff was not exposed
10	0.0003
20	1.0×10^{-6}
30	1.5×10^{-8}
50	2.9×10^{-11}
75	1.0×10^{-13}
100	1.4×10^{-15}
200	2.3×10^{-20}
300	2.6×10^{-23}
400	1.9×10^{-25}
500	4.1×10^{-27}

Opinion 9 (J&J Archive U.S. Containers).

38. Depending on each plaintiff's usage of Johnson & Johnson talcum powder containers, the number of asbestos-containing containers each plaintiff was exposed to is as follows:

Number of Containers Used	95% Prediction Interval for Number of Asbestos-containing containers
10	(3 , 10)
20	(8 , 19)

30	(14 , 27)
50	(25 , 44)
75	(39 , 65)
100	(54 , 86)
200	(111 , 170)
300	(168 , 254)
400	(226 , 338)
500	(283 , 422)

39. Depending on each plaintiff's usage of Johnson & Johnson Baby Powder containers, the number of asbestos-containing containers each plaintiff was exposed to is as follows:

Number of Containers Used	95% Prediction Interval for Number of Asbestos-containing containers
10	(2 , 10)
20	(6 , 18)
30	(11 , 27)
50	(20 , 44)
75	(31 , 65)
100	(43 , 86)
200	(89 , 169)
300	(135 , 253)
400	(181 , 336)
500	(227 , 420)

40. These 95% intervals are constructed so that 95% of such intervals contain the corresponding true value. Thus, for example, if a plaintiff used 20 containers, the number of those containers with asbestos is between 6 and 18 with 95% "confidence."

Opinion 10 (Outside J&J Archive U.S. Containers).

41. These essentially could not be the only 38 containers of Johnson & Johnson talcum powder that contain asbestos.
42. Suppose n Johnson & Johnson talcum powder containers were ever produced. What is the probability that a sample of 57 would find the only 38 that exist?

n	Probability of finding the only 38
100	1.1×10^{-13}
1,000	6.8×10^{-55}
10,000	3.6×10^{-93}
100,000	3.4×10^{-131}
1,000,000	3.3×10^{-169}

10,000,000	3.3×10^{-207}
100,000,000	3.3×10^{-245}
1,000,000,000	3.3×10^{-283}

43. These essentially could not be the only 37 Johnson & Johnson Baby Powder containers that contain asbestos.
44. Suppose n Johnson's talcum Baby Powder containers were ever produced. What is the probability that a sample of 56 would find the only 37 that exist?

n	Probability of finding the only 37
100	1.2×10^{-13}
1,000	1.1×10^{-53}
10,000	6.2×10^{-91}
100,000	5.9×10^{-128}
1,000,000	5.8×10^{-165}
10,000,000	5.8×10^{-202}
100,000,000	5.8×10^{-239}
1,000,000,000	5.8×10^{-276}

45. For comparison purposes, the probability of winning the Powerball Lottery is 3.4×10^{-9} .

Opinion 11 (Outside J&J Archive U.S. Containers).

46. Suppose a plaintiff used n Johnson & Johnson talcum powder containers. What is the probability that this plaintiff was *never* exposed to asbestos?

n	Probability plaintiff was not exposed
10	8.1×10^{-5}
20	4.7×10^{-8}
30	9.6×10^{-11}
50	4.6×10^{-15}
75	3.2×10^{-19}
100	1.6×10^{-22}
200	1.6×10^{-31}
300	2.6×10^{-37}
400	1.4×10^{-41}
500	5.5×10^{-45}

47. Suppose a plaintiff used n Johnson & Johnson Baby Powder containers. What is the probability that this plaintiff was *never* exposed to asbestos?

<i>n</i>	Probability plaintiff was not exposed
10	9.5×10^{-5}
20	6.3×10^{-8}
30	1.5×10^{-10}
50	8.7×10^{-15}
75	7.5×10^{-19}
100	4.4×10^{-22}
200	7.1×10^{-31}
300	1.6×10^{-36}
400	1.1×10^{-40}
500	5.4×10^{-44}

Opinion 12 (Outside J&J Archive U.S. Containers).

48. Depending on the plaintiffs' usage of Johnson & Johnson talcum powder containers, the number of asbestos-containing containers each plaintiff was exposed to is as follows:

Number of Containers Used	95% Prediction Interval for Number of Asbestos-containing containers
10	(2 , 10)
20	(7 , 18)
30	(12 , 26)
50	(23 , 42)
75	(36 , 62)
100	(49 , 81)
200	(101 , 160)
300	(154 , 239)
400	(207 , 318)
500	(260 , 396)

49. Depending on the plaintiffs' usage of Johnson & Johnson Baby Powder containers, the number of asbestos-containing containers each plaintiff was exposed to is as follows:

Number of Containers Used	95% Prediction Interval for Number of Asbestos-containing containers
10	(2 , 9)
20	(7 , 18)
30	(12 , 26)
50	(22 , 42)
75	(35 , 61)
100	(48 , 81)

200	(100 , 159)
300	(152 , 238)
400	(204 , 316)
500	(256 , 394)

50. These 95% intervals are constructed so that 95% of such intervals contain the corresponding true value. Thus, for example, if a plaintiff used 20 containers, the number of those containers with asbestos is between 7 and 18 with 95% “confidence.”

Opinion 13 (Source-specific).

51. Depending on the plaintiffs’ usage of Johnson & Johnson talcum powder containers with **Italian**-sourced talc (19 contaminated out of 35), the number of asbestos-containing containers each plaintiff was exposed to is as follows:

Number of Containers Used	Probability plaintiff was not exposed	95% Prediction Interval for Number of Asbestos-containing containers
10	0.002	(1 , 9)
20	1.4×10^{-5}	(4 , 16)
30	3.3×10^{-7}	(8 , 24)
50	9.5×10^{-10}	(15 , 38)
75	4.2×10^{-12}	(24 , 56)
100	6.2×10^{-14}	(33 , 74)
200	9.3×10^{-19}	(70 , 145)
300	8.8×10^{-22}	(106 , 216)
400	5.4×10^{-24}	(143 , 287)
500	9.9×10^{-26}	(179 , 359)

52. Depending on the plaintiffs’ usage of Johnson & Johnson talcum powder containers with **Vermont**-sourced talc (33 contaminated out of 40), the number of asbestos-containing containers each plaintiff was exposed to is as follows:

Number of Containers Used	Probability plaintiff was not exposed	95% Prediction Interval for Number of Asbestos-containing containers
10	1.9×10^{-6}	(4 , 10)
20	2.1×10^{-10}	(10 , 20)
30	1.9×10^{-13}	(17 , 29)
50	4.4×10^{-18}	(30 , 48)
75	2.6×10^{-22}	(47 , 71)
100	1.5×10^{-25}	(64 , 94)
200	4.6×10^{-34}	(131 , 187)

300	2.3×10^{-39}	(198 , 280)
400	3.2×10^{-43}	(265 , 373)
500	3.0×10^{-46}	(332 , 465)

53. Depending on the plaintiffs' usage of Johnson & Johnson talcum powder containers with **Chinese**-sourced talc (23 contaminated out of 35), the number of asbestos-containing containers each plaintiff was exposed to is as follows:

Number of Containers Used	Probability plaintiff was not exposed	95% Prediction Interval for Number of Asbestos-containing containers
10	0.0002	(2 , 10)
20	4.5×10^{-7}	(6 , 18)
30	3.7×10^{-9}	(11 , 26)
50	2.4×10^{-12}	(20 , 43)
75	2.9×10^{-15}	(32 , 63)
100	1.6×10^{-17}	(44 , 83)
200	1.9×10^{-23}	(92 , 164)
300	3.9×10^{-27}	(140 , 245)
400	8.0×10^{-30}	(187 , 326)
500	6.2×10^{-32}	(235 , 407)

54. Depending on the plaintiffs' usage of Johnson & Johnson talcum powder containers with **Asian**-sourced talc (7 contaminated out of 9), the number of asbestos-containing containers each plaintiff was exposed to is as follows:

Number of Containers Used	Probability plaintiff was not exposed	95% Prediction Interval for Number of Asbestos-containing containers
10	0.0007	(2 , 10)
20	2.3×10^{-5}	(6 , 20)
30	2.3×10^{-6}	(10 , 30)
50	1.1×10^{-7}	(18 , 49)
75	7.9×10^{-9}	(28 , 74)
100	1.2×10^{-9}	(38 , 98)
200	1.2×10^{-11}	(78 , 195)
300	7.2×10^{-3}	(117 , 292)
400	1.0×10^{-13}	(157 , 390)
500	2.1×10^{-14}	(197 , 487)

Assumptions

55. With respect to the presence of asbestos, the various samples of containers analyzed above are not biased.

56. The various samples of containers analyzed above are representative of the respective populations of containers ever produced.

Discussion of the Assumptions

57. The use of a sample to make inference about a population represents the central pillar of statistical practice. The sample produces an “estimate” of a numerical characteristic of the population (such as the proportion with a given trait). A “simple random sample” provides mathematical guarantees of unbiasedness as well as a margin of error with known operating characteristics (e.g., a 95% confidence interval that “covers” the population proportion exactly 95% of the time). The generation of a simple random sample requires an enumeration of every member of the population and every member has a chance, however small, to be included in the sample. Unfortunately, in practice, simple random samples are uncommon. In healthcare, for example, it is essentially never possible to enumerate all people in the world with a given medical condition. Instead, a typical healthcare study recruits patients at a given medical center or set of medical centers. Statisticians still use the machinery of statistical and probabilistic inference to generalize from these (non-random) samples of patients to the general patient population. The underlying notion here is that the sample, while not a random sample, is “representative” of the larger population. A representative sample is one which is drawn without bias from the population of interest. For example, a study of a treatment for atrial fibrillation might recruit patients in New York, but since there is no reason to believe that atrial fibrillation behaves differently in California, physicians would apply the New York results to guide patient care in California. Similarly, a study conducted in 2015 would routinely guide care for patients in 2019 even though today’s patients could not possibly have been included in the 2015 study.
58. No mathematical test for “representativeness” exists. Instead, what statisticians primarily concern themselves with is the potential for bias; could the non-random sample yield biased results? “Sampling variability” means that different samples can and do yield different estimates. This is not the issue. Bias concerns the average behavior across many samples. To make this more concrete, consider the population of all baby powder containers that have ever been produced. Note that a simple random sample is clearly infeasible in this context since we can neither enumerate nor locate all the containers. Denote by p , the proportion of the containers in this population that contain asbestos. Evidently p is a number between zero and one. Any sample of containers can produce an estimate of p . For example, if a sample of 50 containers contains 20 with asbestos, the corresponding estimate would be 0.4. Even if this were a simple random sample of containers, no one expects that p is exactly 0.4. In fact, another sample of 50 containers might yield 25 with asbestos and a corresponding estimate of 0.5. Bias concerns the average of this hypothetical stream of estimates. If the sampling process systematically selects containers that are more likely than containers in general to contain asbestos, the average of the stream of estimates will be bigger than p . This is upwards bias. Similarly, If the sampling process systematically selects containers that are less likely than containers in general to contain asbestos, the average of the stream of estimates

will be smaller than p . This is downwards bias. Neither type of bias is desirable. However, if the sampling process is independent of and oblivious to the asbestos state of the containers it chooses to include, this will ensure that the average of the stream of estimates will be precisely p , the very definition of an unbiased estimate.

59. In order for the sampling process to yield a biased estimate (let's say biased upwards), the process would need to systematically include containers with a higher propensity than others to contain asbestos. Could this happen? Hypothetically, suppose containers produced in even-numbered years had a high propensity to contain asbestos and containers produced in odd-numbered years had a low propensity. If the sampling process only selected containers from even-numbered years, a biased estimate would ensue. However, the samples are known to cover a broad swath of years including the 1960's, the 1970's, the 1980's, and the 1990's. Even if the propensity to contain asbestos ebbed and flowed over the years, to introduce bias, both the lawyers and J&J would need to have sampled containers from the "high" years and avoided the "low" years, all the while with J&J claiming that no asbestos was present at all.

60. I now consider the containers included in my analyses in more detail:

- 1) The first report from MAS that I considered analyzed containers of baby powder spanning many years. Three different law firms obtained these containers from multiple sources. More than half of these containers were positive for asbestos. Setting aside a nefarious scheme, there is no rational basis to believe that the sources of these samples would preferentially be asbestos-containing.
- 2) MAS then analyzed a 1978 container produced out of the J&J Museum. This was positive for asbestos; and again, there is no rational basis to speculate that J&J preferentially kept (and produced pursuant to a court order) asbestos-containing baby powder.
- 3) MAS then analyzed many additional samples of talcum powder produced by J&J out of its historical archives pursuant to court order. Asbestos was detected in those containers at an even higher rate. Again, there is no rational basis to speculate that J&J preferentially kept (and produced pursuant to a court order) asbestos-containing talcum powder.

61. Failure to detect asbestos in the sample does not mean there is none present – asbestos may well be present below MAS's detection limit or it may be present in untested powder from a container that MAS classifies as negative. Because I treated the non-detects as negatives, my probability calculations and predictions are conservative.

62. It is my opinion that with respect to asbestos, the sample of containers tested by MAS *is* representative of the population of all containers. The following facts inform this opinion:

- The sample covers a broad swathe of time from the 1920's to the present day,

and includes, for example, every single year from 1962 to 1986.

- The sample includes talc from all of the sources used by J&J during this period.
- J&J provided the majority of the containers.
- No rational basis exists to preferentially select containers that are more likely to contain asbestos than other containers.

Therefore, the probability calculations and predictions I have made using the sample are entirely proper.

Rubino et al.

63. Rubino *et al.*¹ compared mortality rates in a group of talc miners and millers in Pinerolo, Italy to an age-matched group of residents of Alba, Italy. They concluded “By exposed versus controls comparison the observed overall mortality of talc miners and millers is significantly lower than expected.”
64. Rubino *et al.* is an example of an “observational study.” Such studies have well-documented limitations.² A particular concern with the Rubino *et al.* study is the so-called “healthy worker” effect.³ Workers are systematically healthier than non-workers thereby biasing the comparison in Rubino *et al.* In my opinion, this represents a potentially fatal flaw in the Rubino *et al.* study. Furthermore, individual exposure data was not available to the authors, so they assume that everyone in the mine received the same exposure. At best, this is extraordinarily crude. The provenance of even this overall exposure data is unclear, in particular whether it was gathered in the same mine or mines where the workers were. No data are provided to establish that the control subjects were *not* exposed to talc. The follow-up Rubino *et al.*, Coggiola *et al.*, and Pira *et al.*⁴ studies fail to address any of these concerns.

¹ Rubino, G. F., Scansetti, G., Piolatto, G., & Romano, C. A. (1976). Mortality study of talc miners and millers. *Journal of Occupational and Environmental Medicine*, 18(3), 186-193.

² Ioannidis, John PA. "Why most published research findings are false." *PLoS medicine* 2.8 (2005): e124; Madigan, D., Ryan, P. B., Schuemie, M., Stang, P. E., Overhage, J. M., Hartzema, A. G., Suchard, M.A., DuMouchel, W. & Berlin, J. A. (2013). Evaluating the impact of database heterogeneity on observational study results. *American Journal of Epidemiology*, 178(4), 645-651; Madigan, D., Stang, P. E., Berlin, J. A., Schuemie, M., Overhage, J. M., Suchard, M. A., Hartzema, A. G., DuMouchel, W. & Ryan, P. B. (2014). A systematic statistical approach to evaluating evidence from observational studies. *Annual Review of Statistics and Its Application*, 1, 11-39.

³ Rothman, K. J., Greenland, S., & Lash, T. L. (Eds.). (2008). *Modern Epidemiology*. Lippincott Williams & Wilkins, p.109.

⁴ Rubino, G. F., Scansetti, G., Piolatto, G., & Gay, G. (1979). Mortality and morbidity among talc miners and millers in Italy. *Dusts and disease. Park Forest South, Illinois: Pathodox Publisher, Inc*, 257-363; Coggiola, M., Bosio, D., Pira, E., Piolatto, P. G., Vecchia, C. L., Negri, E., ... & Bacaloni, A. (2003). An update of a mortality study of talc miners and millers in Italy. *American journal of industrial medicine*, 44(1), 63-69; Pira, E., Coggiola, M., Ciocan, C., Romano, C., La Vecchia, C., Pelucchi, C., & Boffetta, P. (2017). Mortality of talcum miners and millers from Val Chisone, Northern Italy: An updated cohort study. *Journal of Occupational and Environmental Medicine*, 59(7), 659-664.

65. Concerning mesothelioma in particular, the Rubino *et al.* study lacks statistical power. Statistical power is the probability of finding a statistically significant difference between exposed and control subjects when one truly exists. Assuming a 40-year working life for the 1,784 exposed workers in Rubino *et al.*, and assuming an annual background rate of 2 mesothelioma cases per 100,000 people,⁵ the power to detect a doubling of the risk is 2.0%. The power to detect a quadrupling is 21.2%. I provide the corresponding R code in Appendix A. Thus, the Rubino *et al.* study would almost certainly not be able to find a substantial difference in mesothelioma rates between “exposed” and “unexposed” subjects, if one existed. The study provides no meaningful scientific evidence with regards to mesothelioma.
66. Ideally, the background rate for the power calculation above would reflect what the mesothelioma rate was in Rubino *et al.*’s control town, Alba. Rubino *et al.*, noted that Alba has a “dominant traditional agricultural activity and very little industrial development not involving any obvious hazard of occupational diseases or carcinogenesis to its workers.” Marinaccio *et al.* (2012) do provide a mesothelioma rate for both Italy as whole (male rate is 3.49 per 100,000) and for Piedmont (male rate is 5.56 per 100,000).⁶ However, Marinaccio *et al.* also note that 81.5% of interviewed male mesothelioma cases in Italy “exhibit an occupational exposure,” suggesting that the rate in Alba might be closer to 1 per 100,000 and certainly smaller than the rate I used above.
67. The choice of 2 per 100,000 in paragraph 54 above is conservative in the sense that it includes both exposed and unexposed individuals. Several authors have estimated the unexposed rate and suggest a rate of 1-2 cases per 1,000,000 person years.⁷ Teta *et al.* utilized SEER data through 2002. I extended their analysis through 2016 producing an estimated unexposed rate of 2.1 per 1,000,000. Using this rate as a background rate for calculating the power of the Rubino study yields close to zero for either doubling or a quadrupling of the risk.
68. Marsh *et al.*⁸ provided extended follow-up for the Rubino cohort and three others. They reported the power to detect a 3-fold and 2.5-fold increased risk as 79% and 62% respectively but used a background rate that reflected exposed and unexposed individuals. Using an unexposed rate of 2.1 per 1,000,000, the one-sided power to detect a 3-fold and 2.5-fold increased risk is 18% and 14% respectively. The Table below shows power at various risks.⁹

⁵ <https://seer.cancer.gov/faststat>

⁶ Marinaccio, A., Binazzi, A., Marzio, D. D., Scarselli, A., Verardo, M., Mirabelli, D., ... & Zotti, R. D. (2012). Pleural malignant mesothelioma epidemic: incidence, modalities of asbestos exposure and occupations involved from the Italian National Register. *International Journal of Cancer*, 130(9), 2146-2154.

⁷ Teta, M. J., Mink, P. J., Lau, E., Scurman, B. K., & Foster, E. D. (2008). US mesothelioma patterns 1973–2002: indicators of change and insights into background rates. *European Journal of Cancer Prevention*, 17(6), 525-534; McDonald, J.C. (1985). *Health implications of environmental exposure to asbestos*. Environmental Health Perspectives, 1985. 62: p. 319-328.

⁸ Marsh, G. M., Ierardi, A. M., Benson, S. M., & Finley, B. L. (2019). Occupational exposures to cosmetic talc and risk of mesothelioma: an updated pooled cohort and statistical power analysis with consideration of latency period. *Inhalation toxicology*, 31(6), 213-223.

⁹ This analysis has been accepted to be published in *Inhalation Toxicology*

Assumed True Risk Ratio	Power
2	11%
2.5	14%
3	18%
4	25%

69. The Selevan *et al.*¹⁰ study in Vermont suffers from an even more extreme lack of statistical power and provides no meaningful statistical information about mesothelioma risk. Fordyce et al.¹¹ recently published extended follow-up of this cohort. The authors discovered a mesothelioma case in the cohort and refer to a different earlier case of mesothelioma from Lamm and Starr¹² as being “in the Vermont cohort.” Lamm and Starr state unambiguously “Mesothelioma caused the death of...one Vermont talc man.” Even using the conservative 2 per 100,000 background rate, this represents a borderline statistically significant increased risk, SMR=5.82, 95% confidence interval 0.98 to 19.24, p=0.052. Using the 2.1 per 1,000,000 rate yields a p-value of less than 0.001 (SMR=55.47, 95% confidence interval from 9.30 to 183.3).¹³

Pleurodesis

70. The three pleurodesis studies I was asked to examine are:

Research Committee of the British Thoracic Association. (1979). A survey of the long-term effects of talc and kaolin pleurodesis. *British journal of diseases of the chest*, 73, 285-288.

Lange, P., Mortensen, J., & Groth, S. (1988). Lung function 22-35 years after treatment of idiopathic spontaneous pneumothorax with talc poudrage or simple drainage. *Thorax*, 43(7), 559-561.

Viskum, K., Lange, P., & Mortensen, J. (1989). Long term sequelae after talc pleurodesis for spontaneous pneumothorax. *Pneumologie (Stuttgart, Germany)*, 43(2), 105-106.

¹⁰ Selevan, S. G., Dement, J. M., Wagoner, J. K., & Froines, J. R. (1979). Mortality patterns among miners and millers of non-asbestiform talc: preliminary report. *Journal of Environmental Pathology and Toxicology*, 2(5), 273.

¹¹ Fordyce, T.A., Leonhard, M., Mowat, F.S., and Moolgavkar, S.H. (2019). A 37-year update on mortality patterns in an expanded cohort of Vermont talc miners and millers. *Journal of Occupational and Environmental Medicine*, to appear.

¹² Lamm, S.H. and Starr, J.A. (1988). Similarities in lung cancer and respiratory disease mortality of Vermont and New York State talc workers. Proceedings of the NIOSH-ILO International Pneumoconioses Conference (7th). Part 2. 1576–1581.

¹³ This analysis has been accepted to be published in the *Journal of Occupational and Environmental Epidemiology*.

I note that these studies are featured on a J&J website.¹⁴

71. Collectively, these studies include 316 talc pleurodesis patients with approximately 7,500 patient years of follow-up. Using a conservative background rate of 2 per 100,000, these studies have a statistical power of 9% to detect a doubling and 19% to detect a quadrupling. Using a more realistic rate of 2.1 per 1,000,000 person years, these studies have a statistical power of 6% to detect a doubling and 8% to detect a quadrupling.
72. In addition to the above-stated opinions, I am prepared to answer any hypotheticals, concerning my areas of expertise or related to my above opinions, presented to me at the time of trial. I am also prepared to consider plaintiff-specific exposure data if made available to me.



David Madigan, PhD
Professor of Statistics
February 21st, 2021

¹⁴ <https://www.factsabouttalc.com/litigation>

Appendix A: R code

```

n <- 10^(2:9)
dhyper(81,81,n-81,121)
dhyper(59,59,n-59,93)

#
# Bayesian approach
#
library(extraDistr)
n <- 91
k <- 61
m <- 20 # number of containers she was exposed to
alpha <- 1
beta <- 1
dbbinom(0, m, alpha = alpha + k, beta = beta + n - k) # probabiity of no exposure
jvec <- seq(0, m, by = 1)
probabilities <- pbbinom(jvec, m, alpha = alpha + k, beta = beta + n - k)
jvec[which.max(probabilities>0.025)]
jvec[which.min((1-probabilities)>0.025)]

# 81/121:
# 10 – 3.3e-05 ( 4 , 9 )
# 20 – 3.7e-09 ( 9 , 17 )
# 30 – 1.1e-12 ( 14 , 25 )
# 50 – 8.4e-19 ( 25 , 41 )
# 75 – 3.5e-25 ( 40 , 60 )
# 100 – 1.5e-30 ( 54 , 79 )
# 200 – 2.3e-46 ( 112 , 154 )
# 300 – 2.9e-57 ( 170 , 229 )
# 400 – 1.4e-65 ( 228 , 303 )
# 500 – 2.6e-72 ( 286 , 378 )

# 59/93:
# 10 – 9.5e-05 ( 3 , 9 )
# 20 – 3.3e-08 ( 8 , 17 )
# 30 – 3.1e-11 ( 13 , 25 )
# 50 – 2.2e-16 ( 23 , 39 )
# 75 – 1.2e-21 ( 36 , 58 )
# 100 – 5.5e-26 ( 49 , 76 )
# 200 – 1.9e-38 ( 102 , 149 )
# 300 – 7.8e-47 ( 155 , 222 )
# 400 – 3.7e-53 ( 209 , 294 )
# 500 – 3.0e-58 ( 262 , 367 )

```

65/99:

10 – 5.3e-05 (3 , 9)
 # 20 – 1.1e-08 (8 , 17)
 # 30 – 6.2e-12 (14 , 25)
 # 50 – 1.8e-17 (24 , 40)
 # 75 – 4.1e-23 (38 , 59)
 # 100 – 8.0e-28 (52 , 78)
 # 200 – 2.3e-41 (107 , 153)
 # 300 – 1.7e-50 (163 , 227)
 # 400 – 2.1e-57 (219 , 301)
 # 500 – 5.7e-63 (275 , 376)

44/72:

10 – 0.0002 (3 , 9)
 # 20 – 1.6e-07 (7 , 17)
 # 30 – 3.5e-10 (12 , 24)
 # 50 – 1.4e-14 (22 , 39)
 # 75 – 5.7e-19 (34 , 57)
 # 100 – 1.5e-22 (46 , 75)
 # 200 – 1.6e-32 (95 , 147)
 # 300 – 4.4e-39 (145 , 218)
 # 400 – 5.4e-44 (194 , 290)
 # 500 – 6.6e-48 (244 , 362)

29/49:

10 – 0.0004 (3 , 9)
 # 20 – 8.5e-07 (7 , 17)
 # 30 – 5.3e-09 (11 , 24)
 # 50 – 1.6e-12 (20 , 39)
 # 75 – 6.9e-16 (31 , 57)
 # 100 – 1.5e-18 (42 , 75)
 # 200 – 8.8e-26 (87 , 147)
 # 300 – 2.1e-30 (132 , 219)
 # 400 – 8.5e-34 (177 , 290)
 # 500 – 1.7e-36 (223 , 362)

26/45:

10 – 0.0006 (2 , 9)
 # 20 – 1.7e-06 (6 , 16)
 # 30 – 1.5e-08 (10 , 24)
 # 50 – 7.8e-12 (19 , 38)
 # 75 – 6.1e-15 (29 , 56)
 # 100 – 2.1e-17 (40 , 74)
 # 200 – 5.5e-24 (83 , 145)
 # 300 – 3.6e-28 (126 , 216)

```
# 400 – 3.0e-31 ( 170 , 287 )
# 500 – 1.1e-33 ( 213 , 358 )
```

```
# 14/27:
# 10 – 0.002 ( 2 , 9 )
# 20 – 3.4e-05 ( 5 , 16 )
# 30 – 1.3e-06 ( 8 , 23 )
# 50 – 8.6e-09 ( 15 , 37 )
# 75 – 9.2e-11 ( 23 , 54 )
# 100 – 2.8e-12 ( 31 , 72 )
# 200 – 3.4e-16 ( 65 , 141 )
# 300 – 1.2e-18 ( 99 , 211 )
# 400 – 2.1e-20 ( 133 , 280 )
# 500 – 8.7e-22 ( 167 , 349 )
```

```
#
# Frequentist approach
# Krishnamoorthy, K., & Peng, J. (2011). Improved closed-form prediction
# intervals for binomial and Poisson distributions. Journal of Statistical
# Planning and Inference, 141(5), 1709-1718.
#
n <- 90
k <- 60
m <- 20 # number of containers she was exposed to
```

```
dhyper(0,m,n,k) # probability of no exposure
jvec <- seq(0, m, by = 1)
probabilities <- 1-phyper(k-1,n,m,k+jvec)
jvec[which.max(probabilities > 0.025) - 1]
probabilities <- phyper(k,n,m,k+jvec)
jvec[which.min(probabilities > 0.025) - 1]
```

```
#
# Rubino Power Calculation
#
library(statmod)

background <- 40*(2/100000) # per person
trueRR <- 4
NumPeople <- 1784

# EXACT
```

```
set.seed(1)
power.fisher.test(background*trueRR, background, NumPeople, NumPeople, alpha=0.05,
  nsim=10000, alternative="two.sided")

# APPROX
set.seed(1)
NumSim <- 10000
NumSig <- 0
for (i in 1:NumSim) {
  n1 <- rbinom(1,NumPeople,background*trueRR)
  n2 <- rbinom(1,NumPeople,background)
  mat <- matrix(c(n1,NumPeople-n1,n2,NumPeople-n2),ncol=2)
  chi <- chisq.test(mat)
  if ((mat[1,1]>0) || (mat[1,2]>0)) {
    if (chi$p.value < 0.05) {NumSig <- NumSig + 1}
  }
}
NumSig/NumSim
```

EXHIBIT 14

Pleural and peritoneal mesotheliomas in SEER: age effects and temporal trends, 1973–2005

Suresh H. Moolgavkar · Rafael Meza · Jay Turim

Received: 12 October 2008 / Accepted: 26 February 2009 / Published online: 18 March 2009
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Abstract We analyzed mesothelioma incidence in the Surveillance, Epidemiology, and End Results (SEER) database over the period 1973–2005 using extensions of the age–period–cohort (APC) models. In these analyses, the usual non-specific age effects of the conventional APC models were replaced by hazard functions derived from two multistage models of carcinogenesis, the Armitage–Doll model and the two-stage clonal expansion (TSCE) model. The extended APC models described the incidence data on pleural and peritoneal mesotheliomas well. After adjustment for temporal trends, the data suggest that the age-specific incidence rates of both pleural and peritoneal mesotheliomas are identical in men and women. Driven largely by birth cohort effects, age-adjusted rates of pleural mesothelioma among men rose from about 7.5 per million person-years in 1973 to about 20 per million person-years in the early 1990s and appear to be stable or declining thereafter. Age-adjusted rates of pleural mesothelioma among women have remained more or less constant at about 2.5 per million person-years over the period 1973–2005. Age-adjusted rates for peritoneal mesothelioma in both men (1.2 per million person-years) and women (0.8 per million person-years) exhibit no temporal trends

over the period of the study. We estimate that approximately 94,000 cases of pleural and 15,000 cases of peritoneal mesothelioma will occur in the US over the period 2005–2050.

Keywords Mesothelioma · Asbestosis · Age-specific incidence · Multistage carcinogenesis

Introduction

Mesothelioma has often been called the sentinel malignancy for asbestos exposure. Multiple epidemiological studies among cohorts of workers occupationally exposed to asbestos have reported elevated risks of mesothelioma. While there is still controversy as to whether pure chrysotile exposure, uncontaminated with amphiboles, can cause mesothelioma [1, 2], the evidence clearly shows that amphiboles are far more potent than chrysotile in causing mesothelioma [3–5]. Case-control studies [6, 7] have similarly shown that certain occupations involving exposure to asbestos are associated with an increased risk of mesothelioma. However, the fiber type, whether chrysotile, amphiboles, or a mixture of the two, is not generally reported in these studies.

Price and Ware [8] showed that the temporal trends in mesothelioma incidence among males reflect temporal trends in asbestos use in the United States with a lag of 20–40 years. They used an age–cohort model to analyze mesothelioma incidence in the Surveillance, Epidemiology, and End Results (SEER) database over the period 1973–2000. Their results suggest that age-adjusted rates among males reached a peak around the early to mid-1990s and have remained relatively constant or declined somewhat since then. They reported that the age-adjusted rates

Electronic supplementary material The online version of this article (doi:10.1007/s10552-009-9328-9) contains supplementary material, which is available to authorized users.

S. H. Moolgavkar
Exponent Inc., Bellevue, WA, USA

S. H. Moolgavkar (✉) · R. Meza · J. Turim
Fred Hutchinsons Cancer Research Center, Seattle, WA, USA
e-mail: smoolgav@fhcrc.org

J. Turim
Exponent Inc., Alexandria, VA, USA

for females are much lower and have remained more or less constant over the period of the analyses, 1973–2000. In a more recent paper, Teta et al. [9] examined the SEER data by five-year age groups over the period 1973–2002 and concluded that the temporal trends of incidence rates among men were driven largely by age groups older than 60.

The most common site for malignant mesothelioma is the pleura. However, a small but significant fraction of cases occurs in the peritoneum. In this paper, we extended the analyses of Price and Ware [8] in two ways. First, we considered pleural and peritoneal mesotheliomas separately. Second, we conducted a full age–period–cohort (APC) analysis for each of the sites. It is well known that when all three factors, age, period, and cohort, are used in analyses of registry data, there is a fundamental problem of non-identifiability [10, 11], sometimes referred to as the problem of arbitrary linear trend in the data. We finessed this problem by recognizing that age is the fundamental determinant of cancer incidence and that cohort and period effects modulate the effect of age. Specifically, we replaced the non-specific age effects of traditional APC models by parametric functions derived from multistage models of carcinogenesis. We have previously used this approach for analyses of the incidence of colon cancer [12, 13], pancreatic cancer [13], and esophageal cancer [14] in SEER.

Materials and methods

Incidence data for mesotheliomas of the pleura and peritoneum were obtained from the SEER 9 registry for the years 1973–1992 and from the SEER 13 registry for the years 1993–2005. See the SEER Cancer Statistics Review [15] for details concerning this database. For our analyses, we used the reported incidence of mesothelioma by gender, age, and calendar year in the SEER geographic areas.

The population bases were obtained from the SEER population files (based on the data from the US Census Bureau) by sex and were cross-tabulated by five-year periods over the calendar years 1973–2005 and 5-year age groups (ages from 0–85+). Model fits for each gender included all races. For all years combined, a total of 6,017 male cases (5,562 pleural, 455 peritoneal) and 1,673 female cases (1,291 pleural, 382 peritoneal) were available for the analyses.¹

¹ Incidence data for the same tumor can be downloaded using different coding schemes from the SEER registry. These distinct methods of downloading the data should yield identical numbers. For example, one can download mesothelioma incidence data using either ICD 10 codes (C45.0 for mesothelioma of the pleura and C45.1 for mesothelioma of the peritoneum, including omentum and mesentery), or using site & morphology = ‘peritoneum, omentum and mesentery’ and histology = 9,050–9,059 (mesothelial neoplasms). For peritoneum, these

We have previously presented likelihood-based analyses of the incidence of different cancers in the SEER registry using hazard functions derived from multistage models to replace the non-specific effects of age in the traditional APC models, while secular trends, i.e., period and cohort effects, were modeled in the usual fashion (see [12–14]). Briefly, we model the age-specific incidence (age a) occurring in calendar year j as

$$h_{ij}(a) = b_i c_j h(a),$$

where $h(a)$ is the hazard function derived from a multistage model, c_j is a coefficient that adjusts for calendar year j , and the coefficient b_i adjusts for birth cohort i ($i = j - a$, stratified in 5-year groups; 1885–1889, 1890–1894, ..., 1955–1990, and >1960). Conforming to the SEER database format, we stratify the data in 18 age groups (0–4 years, 5–9 years, ..., 80–84 years, 85+ years) and into seven periods (1973–1975, 1976–1980, ..., 2001–2005). We then fit each of three multistage models to the number of observed mesothelioma cases stratified by age group and calendar year. We obtained parameter estimates for each model by maximizing the likelihood across all age–calendar strata assuming that the number of cases, either pleural or peritoneal, in each stratum is Poisson distributed with mean $N_{ij} * h_{ij}(a)$, where N_{ij} is the population at risk in age group i and birth cohort j , and $h_{ij}(a)$ is as defined above.

We considered three distinct multistage models for the age effects. First, we considered the Armitage–Doll [16] model of carcinogenesis. In this model, the hazard function for mesothelioma is a power of age. Peto [17] considered a similar model for mesothelioma in occupational cohorts exposed to asbestos, in which the hazard function is a power of time since first exposure. We discuss this model below. We also considered the two-stage clonal expansion (TSCE) model proposed by Moolgavkar and Venzon [18] and Moolgavkar and Knudson [19] and a three-stage extension of it as described in earlier papers [12–14].

Footnote 1 continued

two codings yield highly discrepant results, with the latter coding yielding approximately four times as many tumors as the former. For pleura, the appropriate equivalents to these two approaches yield identical numbers. In this manuscript, we present the results of analyses of peritoneal mesothelioma incidence based on the second approach for the following reasons. First, this is the older method of coding and, therefore, probably less susceptible to error. Second, it appears to have been the method used in the papers by Teta et al. [9] and Boffetta [31]. We have also performed the analyses using the data obtained using the first method. Our conclusions regarding trends and model fits remain unchanged. However, our estimated rates for peritoneal mesothelioma and projected number of cases are approximately a fourth of those presented here. We would be happy to share these results with any interested reader.

The Armitage–Doll model (16)

This model has the following form for the hazard (age-specific incidence) function:

$$H(t) = Ct^k,$$

where C and k are constants to be estimated and t is age.

The TSCE model (18, 19)

The two-stage model posits that cells initiated via a Poisson process undergo clonal expansion and malignant conversion via a birth–death–mutation process. The details of this model are presented in a number of publications (18–21). The hazard function for this model is considerably more complicated than that of the Armitage–Doll model. The model has four parameters, the rate of initiation, ν , the rate of division, α , and death, β , of initiated cells, and the rate of malignant conversion, μ . Not all four parameters can be estimated from incidence data alone. We estimated three identifiable parameters as described below. With constant parameters, the hazard function for this model takes the following form:

$$h(t) = \frac{\nu}{\alpha} pq \frac{e^{-qt} - e^{-pt}}{qe^{-pt} - pe^{-qt}},$$

where p and q are the roots of a quadratic equation, with $p + q = g = -(\alpha - \beta - \mu)$ and $pq = \alpha\mu$. We estimated p , q , and $r \equiv \frac{\nu}{\alpha}$, which comprise a set of identifiable parameters. Thus, the TSCE model requires the estimation of one more parameter than the Armitage–Doll model. Note that g is roughly the net rate of proliferation of initiated cells (since μ is a mutation rate and much smaller than α and β), $q \sim \mu/(1 - \beta/\alpha)$, and r is what Fisher has called the index of diversity [22]. More details are provided in the papers referenced above [12–14, 19–21].

We also fit a three-stage extension of the TSCE model to the data as described in earlier papers [12–14].

We fit models to the data by maximizing likelihoods. In the current context, models arising from the use of distinct multistage hazard functions are not hierarchical. We therefore used the Akaike Information Criterion (AIC) to judge the relative fits of the different models.

All analyses were conducted separately for pleural and peritoneal mesotheliomas. At each site, we first fit models separately to male and female data. We began by fitting the conventional APC model in which separate parameters were fit for each age group, birth cohort, and period (not shown). Although this model suffers from parameter non-identifiability problems, the expectation is well defined and the maximized likelihood is unique. As judged by the AIC, models in which non-specific age parameters were replaced by hazard functions from multistage models did better than the conventional APC model (see Table 1). Moreover, the three-stage extension of the TSCE model did no better than the TSCE model and we therefore do not consider it further. The TSCE model consistently described the data better than the Armitage–Doll model as judged by the AIC and we focus here on results of analyses based on the TSCE model. However, since the Armitage–Doll model has the virtue of transparency and simplicity and, moreover, has been in use for more than two decades we discuss the age-specific incidence estimated from that model as well.

Mesothelioma projections

We projected mesothelioma incidence to the year 2050 in the United States using methods similar to those in Price and Ware [8]. First, we projected the US year 2002 population into the future using mortality rates from the US decennial life tables for 1989–1991 [23]. New births statistics from 2002 to 2005 were obtained from the CDC

Table 1 Parameter estimates and 95% confidence intervals of the TSCE and Armitage–Doll models fits to pleural and peritoneal mesothelioma incidence in SEER 1973–2005

Model	Parameter	Pleura	Peritoneal
TSCE	r	2.80×10^{-4} ($2.30, 3.41$) $\times 10^{-4}$	3.17×10^{-5} ($2.41, 4.18$) $\times 10^{-5}$
	$-p$	0.12 (0.114, 0.127)	0.11 (0.096, 0.13)
	q	1.40×10^{-5} ($1.04, 1.90$) $\times 10^{-5}$	1.78×10^{-4} ($0.98, 3.24$) $\times 10^{-4}$
	AIC^a	−24603	1390.6
Armitage–Doll	C	3.36×10^{-15} ($1.41, 7.99$) $\times 10^{-15}$	1.75×10^{-11} ($0.56, 5.50$) $\times 10^{-11}$
	k	5.14 (4.95, 5.34)	2.79 (2.53, 3.08)
	AIC^a	−24532.2	1424.4

Wald confidence intervals were estimated on logit transformed parameters and then back transformed to the original scale

^a Akaike information criterion

Age-cohort model AIC: pleural mesothelioma = −24578.24, peritoneal mesothelioma = 1429.7

Age-period-cohort model AIC: pleural mesothelioma = −24576.74, peritoneal mesothelioma = 1446.4

National Vital Statistics System (see <http://www.cdc.gov/nchs/births.htm> and [24]). For future years, we assumed that the number of births in each year is equal to those in 2005.

Future birth cohort and calendar year coefficients were assumed to equal the last estimated value.

Results

Table 1 shows the parameter estimates together with the AIC of the Armitage–Doll and TSCE models. We also fit the traditional age–cohort and APC models to the male and female data sets separately and computed the AICs for these models. The AICs for the conventional age–cohort and APC models are reported in the legend to Table 1. Recall that the smaller the AIC, the better the fit of the model. By this criterion, the TSCE model is the best model for both pleural and peritoneal mesotheliomas. The Armitage–Doll model fit is worse than the conventional models for pleural mesothelioma but better for peritoneal mesothelioma.

Figure 1 shows the age-adjusted (to the 2000 US population) mesothelioma incidence in SEER over the period 1973–2005 and the predictions made by our preferred models (see below).

Pleural mesothelioma

Based on the AIC, the incidence of pleural mesothelioma in SEER is described best by a model that postulates a

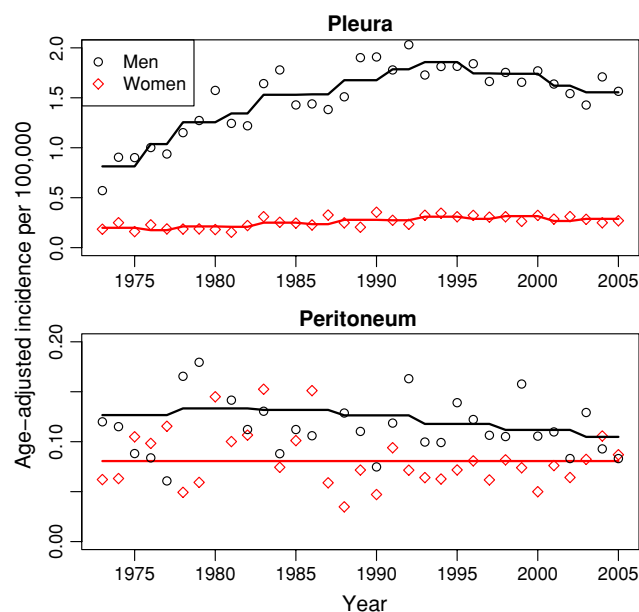


Fig. 1 Observed and expected age-adjusted incidence rates over the period 1973–2005. *Upper panel:* pleural mesothelioma; *lower panel:* peritoneal mesothelioma

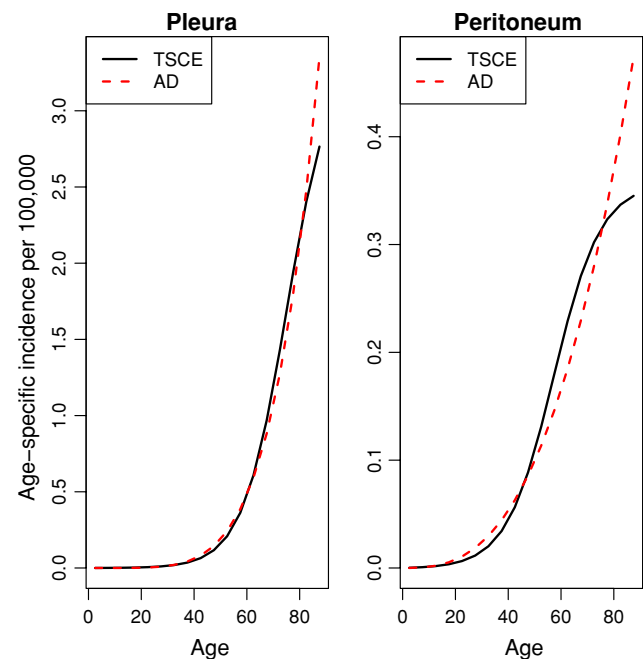


Fig. 2 Age-specific incidence curves generated by the Armitage–Doll and TSCE models. These curves represent the estimated hazard functions of these models multiplied by 100,000. *Left panel:* pleural mesothelioma. See the text for details of the constraints required for identifiability of the incidence curve for pleural mesothelioma. *Right panel:* peritoneal mesothelioma. No constraints are required for the generation of these curves since cohort effects for women are all equal to 1

common age-specific incidence curve for males and females, with separate birth cohort and period effects in the two sexes. Figure 1 shows the age-adjusted rates in the SEER data together with the rates predicted by the TSCE model. This figure shows that the age-adjusted incidence among males rose rapidly from 1973 to about 1990 when it reached a peak. There is a hint of a decline beginning in the early 1990s. The age-adjusted incidence among females appears to be more or less constant over the entire period of observation. Figure 2 shows the estimated age-specific incidence curves using the TSCE and Peto models. Temporal trends are dominated by strong cohort effects, especially among men (Fig. 3). The first three cohort effects estimates in females were almost equal to one another and had large confidence intervals, as did the last three. In the final models, the first three cohort effects for females were set equal to one another as were the last three, leading to a total of 12 cohort effects parameters in females and 16 in males. The cohort effects are modulated by period effects (Fig. 4) that are more or less constant for males, but decline modestly for females (Fig. 5). Figure 6 shows the lifetime probability of developing mesothelioma by birth year adjusted for survival from other causes of mortality (US decennial life tables for 1989–1991). Figure 7 shows the lifetime probability unadjusted for other

cause mortality. These figures indicate that, over the period of observation, the lifetime probability of pleural mesothelioma among men showed a rapid increase by birth cohort until the cohort of the early 1920s, following which there was an equally rapid decline. These trends clearly reflect the trends in birth cohort effects shown in Fig. 3. Among females, there is a more modest increase and lifetime risks appear to have stabilized. Interestingly, male

and female lifetime probabilities are virtually identical in the earliest and latest birth cohorts.

Peritoneal mesothelioma

The incidence of peritoneal mesothelioma in SEER is described best by a model that postulates common

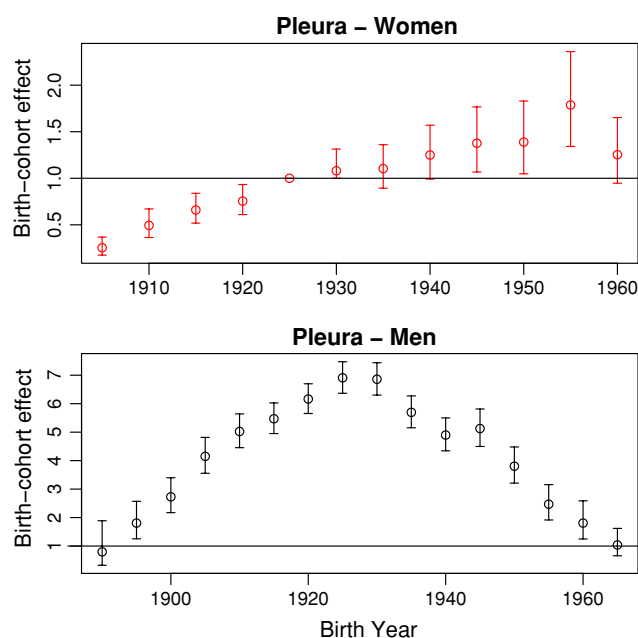


Fig. 3 Birth-cohort effects and 95% confidence intervals for pleural mesothelioma. *Upper panel: women; lower panel: men*

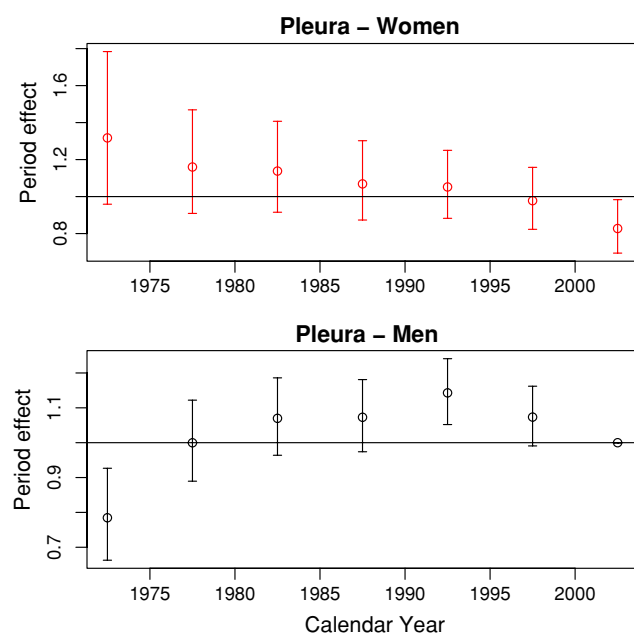


Fig. 4 Period effects and 95% confidence intervals for pleural mesothelioma. *Upper panel: women; lower panel: men*

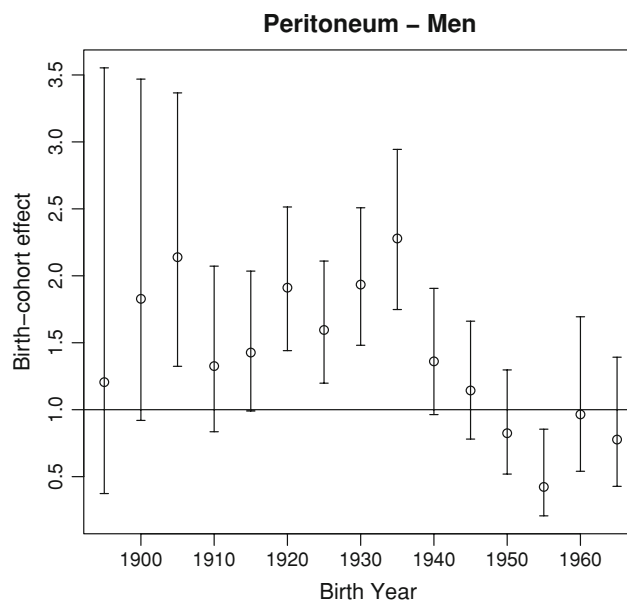


Fig. 5 Birth-cohort effects and 95% confidence intervals for peritoneal mesothelioma among men

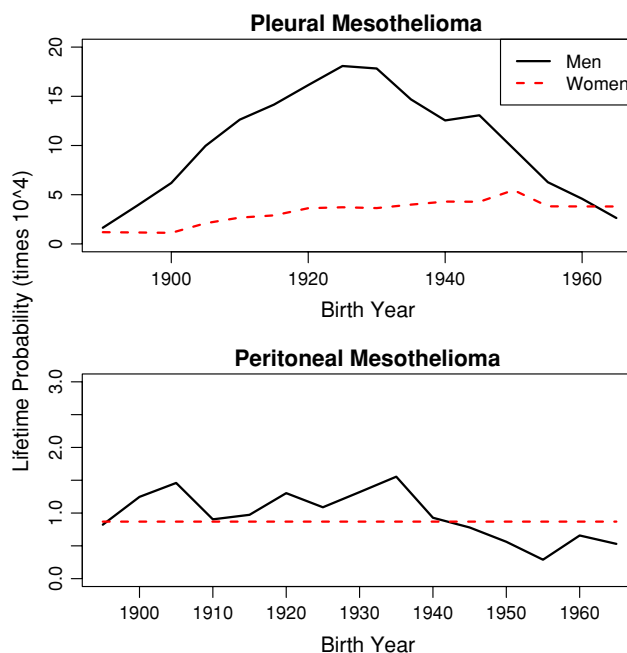


Fig. 6 Lifetime probability of mesothelioma by birth cohort after adjustment for other cause mortality. *Upper panel: pleural mesothelioma; lower panel: peritoneal mesothelioma*

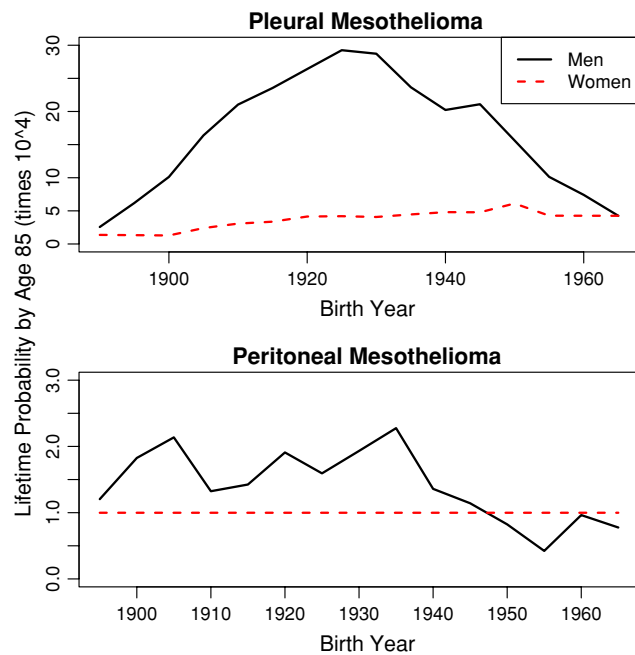


Fig. 7 Lifetime probability of mesothelioma by birth cohort without adjustment for other cause mortality. *Upper panel:* pleural mesothelioma; *lower panel:* peritoneal mesothelioma

age-specific incidence rates in males and females with birth cohort effects identically equal to one among females and period effects identically equal to one in both genders. The estimated cohort effects among males have wide confidence intervals, but suggest a pattern similar to the cohort effects for pleural mesothelioma among males. Thus, the data are consistent with no secular trends in peritoneal mesothelioma incidence among women and only weak trends among men over the period 1973–2005. Figure 2 shows the age-specific incidence curves for peritoneal mesothelioma generated by the Armitage–Doll and the TSCE models. Since there have been no temporal trends, the lifetime probability of peritoneal mesothelioma among women, adjusted for other cause mortality, is constant at approximately 1×10^{-4} over all the birth cohorts in the data. Among men, this probability lies between 1×10^{-4} and 1.5×10^{-4} for all birth cohorts (Fig. 6). The lifetime probability (to age 85) unadjusted for other cause mortality is about 1×10^{-4} among women and ranges between 1×10^{-4} and 2.5×10^{-4} among men (Fig. 7).

Projected incidence

The total numbers of incident cases of pleural and peritoneal mesothelioma in the US projected to the year 2050 are shown in Fig. 8.

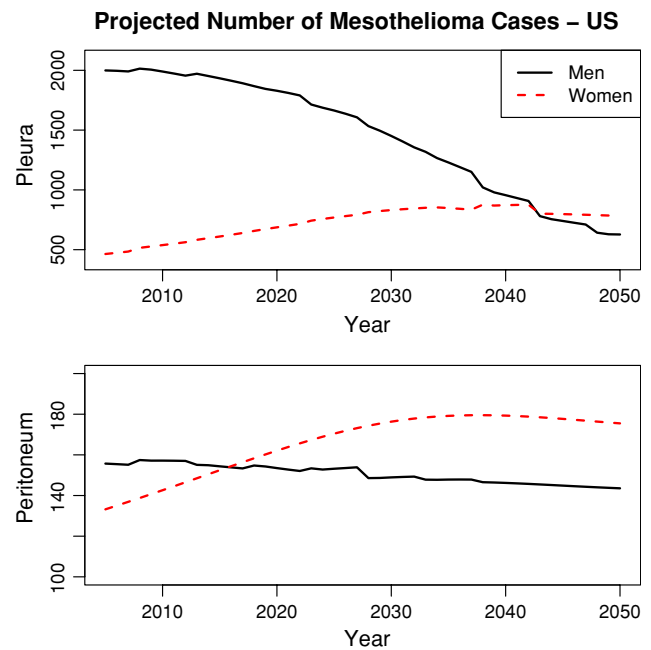


Fig. 8 Projected number of mesothelioma cases in the US to the year 2050. *Upper panel:* pleural mesothelioma; *lower panel:* peritoneal mesothelioma

Discussion

In this paper, we have used APC models to investigate age effects and temporal trends in mesothelioma incidence in SEER, with the non-specific age effects of traditional APC models replaced by parametric incidence curves based on the ideas of multistage carcinogenesis. Both the Armitage–Doll and TSCE models describe the data well within this analytic framework. The age effects isolated by this procedure approximate the age-specific incidence curves of pleural and peritoneal mesotheliomas after adjustment for temporal trends that are largely due to asbestos exposure, although other factors could be involved. We have also used a number of assumptions to project mesothelioma incidence in the US to the year 2050.

Age-specific incidence

As seen in Fig. 2, the incidence curves predicted by the two models are similar, with the Armitage–Doll model predicting somewhat higher incidence rates at the older ages. For pleural mesothelioma, the exponent k of the Armitage–Doll model is estimated to be ~ 5 as shown in Table 1.

Peto et al. [17] in an analysis of the insulator database found that the mortality rates among those continuously exposed was described well by a model in which duration of exposure is lagged by 10 years and raised to the power 3.2. However, in a document prepared for the U.S. EPA in 1986 [25], Nicholson pointed out that Peto et al. [16]

excluded workers who entered the workforce before 1922 and after 1946 and who were over the age of 80. For the entire cohort, Nicholson found that a model with time since first exposure raised to the power 5 described the data well.

Nicholson et al. [26] estimated the number of mesotheliomas that could be expected for different occupations from 1980 through 2030, using data from the insulator cohort to estimate the parameters of the mortality rate as function of time since first exposure, which he also assumed to be proportional to time raised to a power. He found that the risk of death increased as the fourth or fifth power of time from onset of exposure for about 40 or 50 years, without giving a precise value of the exponent. We estimate from the data presented in the Nicholson paper that the exponent is about 4.5. Thus, the value of the exponent of the Armitage–Doll model given by the modified APC approach used here is consistent with values found in the literature. It should be kept in mind, however, that in the model here it is the age that is raised to the power 5, whereas in the analyses of Peto and Nicholson it is time since first exposure.

An analogous situation obtains with lung cancer. Doll and Peto [27] have reported that lung cancer mortality rates increase with between the fourth and fifth power of age among non-smokers and with a similar power of duration of smoking among smokers. The multiplicative parameter C in the Armitage–Doll model is not uniquely identifiable in an APC model because the estimate of this parameter depends upon which of the cohort or period parameters is anchored at 1. For the same reason, although v/α is an identifiable parameter of the TSCE model, when the TSCE model is embedded in an APC model, this parameter is identifiable only up to a multiplicative non-zero constant. In these analyses, the parameters for the birth cohort 1926–1930 for women and the period 2001–2005 for men were constrained to be 1. Then the parameters C and v/α are identifiable. The age-specific incidence curves in Fig. 2 are based on this choice of constraints.

For peritoneal mesothelioma the exponent is close to 3 and so is smaller than the exponent for pleural mesothelioma. There are no analyses of peritoneal mesothelioma comparable to the analyses of Peto and Nicholson discussed above.

Within the framework of the Armitage–Doll model, these results suggest that approximately six and four mutations, respectively, are involved in the genesis of pleural and peritoneal mesotheliomas. Moreover, the constant C , which is the product of the number of cells at risk and the mutation rates, is considerably larger in peritoneal than in pleural mesothelioma (Table 1). This finding is to be expected since C involves the product six mutation rates, each much smaller than 1, for pleural mesothelioma, and only four mutation rates for peritoneal mesothelioma.

Within the framework of the TSCE model, these results suggest that the higher age-specific incidence of pleural mesothelioma can be mainly attributed to a higher index of diversity r , due either to a higher background initiation rate, v , or a lower rate of cell division, α , or both. The initiation rate, v , depends both on the number of target cells and on the rate of the initiating mutation.

For peritoneal mesothelioma, the age-specific incidence curves in Fig. 2 can be interpreted to be the best estimates from the SEER data of the incidence in a population unexposed to asbestos. For pleural mesothelioma, the age-specific incidence curves represent the best estimate of the age distribution of pleural mesothelioma incidence in a population unexposed to asbestos, but the actual magnitude of the age-specific incidence rates is not identifiable.

Temporal trends

Over the period of this study, there have been no secular trends in peritoneal mesothelioma among women and only weak trends among men. This observation suggests that asbestos exposure was responsible for only a minor fraction of peritoneal mesotheliomas in SEER over the period 1973–2005. Spirtas et al. [6] reported that about 58% of peritoneal mesotheliomas among men in their study population were attributable to asbestos exposure. For females, they were unable to estimate separate attributable fractions for pleural and peritoneal mesotheliomas, but reported that the attributable fraction for both sites combined was 23%. Our results here suggest that, at least in the SEER data over the period of observation, the attributable fraction for male peritoneal mesotheliomas was lower than that reported by Spirtas.

Similar results have been reported in other registries. Hemminki and Li [28] examined trends in the incidence of peritoneal mesothelioma in Sweden over the period 1961–1998. Among men they reported that only 29% had “typical asbestos-related jobs...” Interestingly, the age-adjusted incidence rates were virtually identical in men and women. Since men are much more likely to be occupationally exposed to asbestos, this finding suggests that a large fraction of peritoneal mesotheliomas in Sweden over this period were unrelated to asbestos exposure. Moreover, the generally increasing trends in incidence over this period are probably attributable to factors other than asbestos.

Burdorf et al. [29] examined the incidence of peritoneal mesothelioma among men and women in Sweden and the Netherlands over the period 1989–2003 and reported absence of any trends. They concluded, “[t]he absence of a time trend in the incidence rate of peritoneal mesothelioma in Sweden and the Netherlands in the past 15 years may point to a more limited role of occupational exposure to asbestos in the etiology of peritoneal mesothelioma than for pleural mesothelioma, especially among women.”

Seidman and Selikoff [30] reported 282 peritoneal mesotheliomas out of a total of 453 mesotheliomas in the cohort of US and Canadian insulators. One would expect to see such a large number of cases reflected in the temporal trends in peritoneal mesothelioma rates in a population-based registry. Why then do we observe only weak temporal trends in peritoneal mesothelioma incidence among men in the SEER database over the period 1973–2005? The 282 peritoneal mesotheliomas reported by Seidman and Selikoff occurred over the 20-year period 1967–1986. Some fraction of these occurred in Canada and thus would not be reflected in the US statistics. Moreover, some fraction of the US cases occurred prior to 1973 and would thus not be reflected in the SEER database starting in 1973. Finally, SEER represents only about 10% of the US population. Thus, one would expect the peritoneal mesotheliomas in the insulators' cohort to have only a small impact on temporal trends in the SEER registry over the period 1973–2005.

In a recent review of the epidemiology of peritoneal mesothelioma, Boffetta [31] reported that there was a strong correlation between the fraction of deaths from pleural and peritoneal mesothelioma in cohorts occupationally exposed to high levels of asbestos. This finding suggests that occupational exposure to asbestos can increase the risk of both pleural and peritoneal mesothelioma. In contrast, Boffetta reported low correlation between the incidence of pleural and peritoneal mesothelioma in population-based registries. This finding suggests that, in the general population, a smaller fraction of peritoneal than pleural mesothelioma is attributable to asbestos exposure.

As reported by Price and Ware [8], trends in pleural mesotheliomas among men clearly reflect temporal trends in asbestos use in the US. There has been a strong cohort-wise increase in the rates of pleural mesotheliomas among men reaching a peak with the birth cohorts of the early 1920s and declining thereafter. The birth cohort of 1965 appears to have approximately the same risk as that of 1890, so that by the cohort of 1965 the epidemic of asbestos-induced pleural mesothelioma appears to have abated. Among women, the birth cohort effects appear to have increased, albeit much slower than among the men, until about the cohort of 1925. The birth cohort effects appear to be more or less flat from 1925 to 1965. As reported earlier in 'Results', period effects are declining slightly among the women, which contributes to the generally flat age-adjusted incidence rates despite the increase in birth cohort effects. We note here that information on the earliest and latest cohorts among men are based on few observations so that conclusions about them must be made with caution.

The differences in the patterns of birth cohort and period effects between males and females suggest that factors

other than asbestos exposure are responsible, in part, for the observed temporal trends.

Figures 6 and 7 show the lifetime probabilities of developing pleural and peritoneal mesothelioma by birth cohort adjusted and unadjusted for other cause mortality, respectively. It is of interest to note that the lifetime probabilities in males and females are similar in the earliest and latest birth cohorts, suggesting a beginning and an end to the epidemic of asbestos-related pleural mesotheliomas.

Background rates

There is some interest in estimating the background rates of pleural and peritoneal mesotheliomas, i.e., the rates that would be expected in the absence of any recorded exposure to asbestos. Background rates are easiest to define for peritoneal mesothelioma since there appear to have been no secular trends among women associated with the use of asbestos in the US, and only weak trends among men. Clearly, incidence rates depend upon age as shown in Fig. 2. Any summary age-adjusted rate depends on the standard population used for the adjustment. With the standard population used in this paper, the age-adjusted background peritoneal mesothelioma rate is approximately 1 per million individuals per year, as indicated in Fig. 1. The lifetime probability of developing peritoneal mesothelioma, when adjusted for other cause mortality, likewise depends on the specific life-table used for the adjustment. With the life tables used in this paper, the lifetime probability of peritoneal mesothelioma is 1 per 10,000 women and between 1 and 1.5 per 10,000 men. These probabilities can be taken to be estimates of the background risks of peritoneal mesothelioma among women and men, respectively.

For pleural mesotheliomas, background rates are more difficult to estimate because there have been secular trends among both men and women. The secular trends among men are clearly dominated by the use of asbestos in the work place, although other factors could also be at play. Among women, birth cohort effects have risen modestly while period effects have declined leading to age-adjusted incidence rates that have remained more or less constant over the period of this study at about 3 per million individuals per year. This observation suggests that, even if some fraction of female cases can be attributed to asbestos exposure, the background rates are between 2 and 3 per million individuals per year. If the pathogenesis of spontaneous pleural mesotheliomas is similar in men and women, a not unreasonable assumption, this range of estimates can be taken to represent estimates of the background rate of pleural mesothelioma in men as well. Thus, the background rates of pleural mesotheliomas appear to be approximately 2–3 times higher than the background rates

of peritoneal mesothelioma. Among men, the cohort-wise life-time probability of pleural mesothelioma, adjusted for other cause mortality, increased from about 2 per 10,000 individuals in the cohort of 1890 to approximately 18 per 10,000 in the cohort of 1925 before decreasing again to about 2 per 10,000 in the cohort of 1965. Among women, over the same period of time, the lifetime probability increased modestly from about 2 per 10,000 in the cohort of 1890 to about 4 per 10,000 in the cohort of 1925 and remained more or less constant in later cohorts. These observations suggest that the background lifetime probability of pleural mesothelioma is approximately 3 per 10,000. Thus, the lifetime probability of pleural mesothelioma is about 2–3 times larger than that of peritoneal mesothelioma. For comparison, Price and Ware [8] estimate that the background lifetime probability of pleural and peritoneal mesothelioma combined is 3.6 per 10,000 individuals.

Projections

Figure 8 shows the number of mesothelioma cases that would be expected to occur in the US under the assumptions discussed above. The top panel shows the number of pleural mesothelioma cases among men and women, whereas the bottom panel shows the number of peritoneal cases over the period 2005–2050. We estimate approximately 62,000 pleural mesotheliomas among men and approximately 32,000 pleural mesotheliomas among women over this period. The corresponding figures for peritoneal mesotheliomas are 7,600 and 6,900, respectively, among men and women. The larger number of pleural mesotheliomas among men reflects the continuing, but declining, impact of asbestos use on pleural mesothelioma. The larger projected number of peritoneal mesotheliomas among women reflects the higher life expectancy of women in the US population. Our projections of the total number of mesotheliomas are in reasonable agreement with those of Price and Ware [8].

Conclusions

Although both pleural and peritoneal mesotheliomas are known to be associated with exposure to amphibole asbestos, the trends in the incidence of peritoneal mesothelioma in both sexes in SEER have not been influenced by the trends in occupational asbestos exposure in the US. In contrast, trends of pleural mesothelioma among men have been strongly influenced by occupational exposure to asbestos. Background incidences and life-time probabilities of mesothelioma at both sites appear to be similar in men and women with these rates for pleural mesothelioma being 2–3 times higher than those for peritoneal mesothelioma.

After adjustment for secular trends, the age-specific incidence of mesothelioma at both sites is well described by the TSCE and Armitage–Doll models.

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EXHIBIT 15



Exponent
15375 SE 30th Place
Suite 250
Bellevue, WA 98007

telephone 425-519-8700
facsimile 425-519-8799
www.exponent.com

March 8, 2021

L. Lucy Willson, Esq.
Willcox & Savage PC
40 Monticello Avenue, Suite 2200
Norfolk, VA 23510

J.T. Larson, Esq.
Barnes & Thornburg LLP
11 S. Meridian Street
Indianapolis, IN 46204-3535

Subject: *Report of Dr. Suresh Moolgavkar – Hirshberg Matter*

Dear Ms. Willson and Mr. Larson,

[REDACTED] For purposes of this report, I have been asked to review the biological process of carcinogenesis, particularly as it applies to malignant mesothelioma, with special emphasis on the role of asbestos exposure in increasing the risk of this disease as it relates to alleged exposure to asbestos from the use of cosmetic talcum powder.

I have also been asked to rebut opinions expressed by Dr. Madigan in cases of malignant mesothelioma allegedly caused by exposure to cosmetic talc. Dr. Madigan's opinions in talc-related litigation fall into three broad areas:

- 1) Dr. Madigan has used Dr. Longo's testing results to opine on the probability that a specific plaintiff was exposed to asbestos from cosmetic talc products. While Dr. Madigan's numerical results have been periodically revised to reflect the number of containers of talc tested by Dr. Longo, his methods and main conclusions have not changed;
- 2) Dr. Madigan has opined on the analyses of temporal trends in mesothelioma incidence in the U.S. and the impact of age on mesothelioma incidence; and
- 3) Dr. Madigan has opined on epidemiologic studies in general, and on the epidemiologic studies of cosmetic talc and mesothelioma, in particular. These opinions have appeared in numerous expert reports written by Dr. Madigan. I refer to several of them in my rebuttal.

In my expert report, I offer rebuttals of each of these three sets of opinions offered by Dr. Madigan in this case specifically (Madigan, 2019a, 2019b, 2020a, 2021) and in the past (Madigan, 2018a,b, 2019c, 2020b, 2020c, 2020d).

EPA used the Peto-Nicholson model for the extrapolation, a procedure that it rejected explicitly for its risk assessment at Libby, Montana. Furthermore, the EPA offers no insights into the magnitude of the extrapolation required for the risk assessment using the textile workers as a surrogate for evaluation of risk in vehicle mechanics. The cumulative asbestos exposures (including both chrysotile and amphiboles) in the North Carolina textile cohort ranged from <0.1 f/ml-year to 1,271.1 f/ml-year. With only four cases of mesothelioma reported in this cohort, the EPA should have sought and provided information on the exposure received by each case of mesothelioma.²⁴ At the very least, the EPA should have offered information by broad ranges of exposure. Did any cases of mesothelioma receive exposure below 100 f/ml-year, for example? In contrast to the mixed fiber exposures reported in textile workers, as discussed earlier in my report, chrysotile asbestos exposures of U.S. vehicle mechanics are reported as less than approximately 3–5 f/ml-years on a cumulative basis (Finley et al., 2007). Finally, the public comments contained numerous criticisms of the EPA's procedures, based on the current science. The EPA did not respond to these comments and suggestions, except to say that it was using EPA procedures that had been used for asbestos risk assessment since 1986, new information notwithstanding.

Dr. Kanarek's²⁵ 2011 paper on chrysotile asbestos (Kanarek, 2011) does not mention any of these multiple epidemiologic studies of vehicle mechanics exonerating exposure to low-level chrysotile asbestos as a cause of mesothelioma. He relies, instead, on a series of case reports and studies based on case reports to support his conclusion that brake repair work increases the risk of developing mesothelioma. His conclusion is as untenable as his methods for arriving at it. In fact, Nicholson et al. (1984) estimated that there were approximately 5,000,000 current and former automobile mechanics in the U.S. at the time of his study. Based on a background rate of three to four per million person-years for spontaneous mesothelioma, one would expect 300 to 400 cases of mesotheliomas to arise spontaneously among automobile mechanics over a 20-year period.

In a later paper, Kanarek and Anderson (2018) consider the case-control studies investigating the association between work as a vehicle mechanic and mesothelioma but dismiss all of them out of hand for perceived methodological deficiencies. The authors go through the ritual motions of applying the Hill criteria to argue that the weight of the evidence suggests that work as a vehicle mechanic is a risk factor for mesothelioma, although they admit that there is no evidence showing even an association, let alone a strong association, between work as a vehicle mechanic and mesothelioma. The Hill criteria were developed to distinguish a causal association from a mere statistical association (Hill, 1965); therefore, without the demonstration of a statistically significant

²⁴ Dr. Loomis, the first author of Loomis et al. (2019), which is the basis of the EPA risk assessment, was a member of the scientific review panel for the risk assessment. The EPA should have sought the raw data from him and conducted an independent analysis, a step that the EPA took in the risk assessment for Libby, Montana.

²⁵ Dr. Kanarek, who serves as a plaintiff's expert, was also a member of the scientific review panel for the risk assessment.

EXHIBIT 16

06/16/2023 - Office Visit in Primary Care - Savage Rd. (continued)**Patient as-of Visit (continued)**

Administered on: 10/27/2008	Dose: 0.5 {mL}	CVX code: 115

TDaP, ADACEL (age 10y-64y), BOOSTRIX (age 10y+), IM, 0.5mL

Administered on: 1/18/2018	Dose: 0.5 {cc}	CVX code: 115
Lot number: 9PD92		

TDaP, ADACEL (age 10y-64y), BOOSTRIX (age 10y+), IM, 0.5mL

Administered on: 3/17/2018	Dose: 0.5 {cc}	CVX code: 115
Lot number: Z9Z4Y		

Notes**Addendum Note****Anthony J Germinario, MD at 6/19/2023 0746**

Author: Anthony J Germinario, MD	Service: —	Author Type: Physician
Filed: 6/19/2023 7:46 AM	Encounter Date: 6/16/2023	Status: Signed
Editor: Anthony J Germinario, MD (Physician)		
Added by: GERMINARIO, ANTHONY J on: 6/19/2023 07:46 AM		

Modules accepted: Orders

Electronically signed by Anthony J Germinario, MD at 6/19/2023 7:46 AM

Progress Notes**Anthony J Germinario, MD at 6/16/2023 0956**

Author: Anthony J Germinario, MD	Service: —	Author Type: Physician
Filed: 6/19/2023 7:46 AM	Encounter Date: 6/16/2023	Status: Addendum
Editor: Anthony J Germinario, MD (Physician)		

Date of Service: 6/16/2023**Patient:** Michael L Perry**DOB:** 12/20/1969**Chief Complaint:** chronic cough, rectal bleeding.**History of Present Illness:**

Michael L Perry a 53 y.o. male presents today for PHYS/WEEL visit but this was transitioned to acute visit.

He has past medical history of insomnia, HLD, chronic back pain, diverticulitis, allergic rhinitis and mild intermittent asthma. Interim blood work is reviewed from 06/15/23. CBC showed WBC 12.0, Hgb 10.7, MCV 78. CMP showed glucose 109, ALP 137, AST 58, ALT 100. Lipid panel showed total cholesterol 127, LDL 83, HDL 34, triglycerides 50. PSA 0.691.

He has history of allergic rhinitis, HLD, anxiety/depression, insomnia, testicular cancer s/p orchiectomy and chemotherapy (1990) and history of low back pain In past year he has made a job switch, now working remotely for a company doing sales and marketing. He is an engineer by trade. Interim blood work is reviewed from 06/12/23. CMP showed glucose 111. Lipid panel showed total cholesterol 181, LDL 106, HDL 48, triglycerides 134.

EXHIBIT 17

Gregory B. Diette, MD, MHS
July 03, 2024

STATE OF SOUTH CAROLINA : IN THE COURT OF COMMON PLEAS
:
COUNTY OF RICHLAND : FOR THE FIFTH JUDICIAL CIRCUIT
MICHAEL L. PERRY and :
LONNIE L. LONG, :
Plaintiffs, : C/A No.
v. : 2023-CP-40-04072
AMERICAN INTERNATIONAL :
INDUSTRIES, et al., :
Defendants. :

CERTIFIED
ORIGINAL

Deposition of
GREGORY B. DIETTE, MD, MHS

Via Zoom Videoconferencing

Wednesday, July 3, 2024
10:00 a.m.

Reported by:
Adam D. Miller, Registered Professional Reporter

Page 2 1 APPEARANCES: 2 On Behalf of Plaintiffs: 3 SAM IOLA, ESQUIRE 4 siola@dobslegal.com 5 DEAN OMAR BRANHAM SHIRLEY, LLP 6 302 North Market Street, Suite 300 7 Dallas, Texas 75202 8 214.722.5990 9 On Behalf of Johnson & Johnson; LLT Management, LLC, 10 formerly known as LTL Management, LLC; Kenvue, Inc.; and 11 Johnson & Johnson Holdco (NA) Inc.: 12 CHRIS COWAN, ESQUIRE 13 Chris.Cowan@butlersnow.com 14 and KIM BUENO, ESQUIRE 15 BUTLER SNOW LLP 16 1400 Lavaca Street, Suite 1000 17 Austin, Texas 78701 18 737.802.1800 19 On Behalf of Avon Products, Inc.: 20 BRUCE T. BISHOP, ESQUIRE 21 bbishop@wilsav.com 22 WILLCOX & SAVAGE 23 440 Monticello Avenue, Suite 2200 24 Norfolk, Virginia 23510 25 757.628.5500	Page 4 1 On Behalf of PTI Union, LLC: 2 E. ELAINE SHOFNER, ESQUIRE 3 eshofner@hpylaw.com 4 HAWKINS PARNELL & YOUNG LLP 5 303 Peachtree Street, N.E., Suite 4000 6 Atlanta, Georgia 30308-3243 7 404.614.7400 8 On Behalf of Walmart, Inc.: 9 RANDI LYNN ROBERTS, ESQUIRE 10 rlroberts@lbrblaw.com 11 LEWIS BLAIN ROBERTS & BOYD, LLC 12 3700 Forest Drive, Suite 400 13 Columbia, South Carolina 29204 14 803.790.8838 15 On Behalf of Bristol-Myers Squibb Company; Calvin Klein, 16 Inc.; Coty, Inc.; Est e Lauder Inc.; Est e Lauder 17 International, Inc.; The Est e Lauder Companies, Inc.; 18 The Procter & Gamble Company; and Shulton Inc.: 19 JAMES B. GLENN, ESQUIRE 20 jase.glenn@cs-law.com 21 COSMICH, SIMMONS & BROWN, PLLC 22 701 Gervais Street 23 Suite 150, PO Box 109 24 Columbia, South Carolina 29201 25 601.255.0856
Page 3 1 On Behalf of C&S Wholesale Grocers, LLC; CVS Health 2 Corporation; CVS Pharmacy Inc.; Piggly Wiggly, LLC; 3 Walgreen Co.; and Food Lion, LLC: 4 AMY HARMON GEDDES, ESQUIRE 5 AGeddes@maynardnexsen.com 6 MAYNARD NEXSEN PC 7 1230 Main Street, Suite 700 8 Columbia, South Carolina 29201 9 Post Office Box 2426 (29202) 10 803.771.8900 11 On Behalf of Chanel, Inc.: 12 CURTIS D. HECKMAN, ESQUIRE 13 checkman@orrick.com 14 ORRICK, HERRINGTON & SUTCLIFFE LLP 15 2121 Main Street 16 Wheeling, West Virginia 26003 17 304.231.2600 18 On Behalf of American International Industries: 19 TIM PECK, ESQUIRE 20 TPeck@foxrothschild.com 21 FOX ROTHSCHILD LLP 22 300 North Greene Street, Suite 1400 23 Greensboro, North Carolina 27401 24 336.378.5200 25	Page 5 1 On Behalf of Vi-Jon, LLC: 2 SHANA E. RUSSO, ESQUIRE 3 srusso@reedsmith.com 4 REED SMITH LLP 5 506 Carnegie Center, Suite 300 6 Princeton, New Jersey 08540 7 609.987.0050 8 On Behalf of PTI Royston, LLC: 9 M. TODD RAINSFORD, ESQUIRE 10 toddrainsford@piercesloan.com 11 PIERCE SLOAN KENNEDY & EARLY LLC 12 321 East Bay Street (29401) 13 P.O. Box 22437 14 Charleston, SC 29413-2437 15 843.722.7733 16 On Behalf of IMI Fabi (Diana), LLC; IMI Fabi (USA), 17 Inc.; and IMI Fabi LLC: 18 THEODORE F. ROBERTS, ESQUIRE 19 Ted.Roberts@wbd-us.com 20 WOMBLE BOND DICKINSON (US) LLP 21 100 Light Street, 26th Floor 22 Baltimore, Maryland 21202 23 410.545.5800 24 25

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DEPONENT: GREGORY B. DIETTE, MD, MHS

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doctor in the Perry matter.

Exhibit 4 is the curriculum vitae that was produced to me.

Exhibit 5 will be the combined Perry invoices.

And then there are documents labeled depos notes, legal notes, and medical notes of the doctor's. Those will be marked -- Exhibit 6 to be depo notes; Exhibit 7 will be legal notes; Exhibit 8 will be the medical notes.

And then, finally, Exhibit 9 will be the prior testimony list.

(Exhibit 1 was marked for identification.)

(Exhibit 2 was marked for identification.)

(Exhibit 3 was marked for identification.)

(Exhibit 4 was marked for identification.)

(Exhibit 5 was marked for identification.)

(Exhibit 6 was marked for identification.)

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GREGORY B. DIETTE, MD, MHS, having first been duly sworn according to law, was examined and testified as follows:

- - - - -

ATTORNEY IOLA: Good morning, Doctor. I had an opportunity to introduce myself before we started. Thank you for making time this morning.

THE WITNESS: Good morning.

ATTORNEY IOLA: I want to go ahead and -- we have a stipulation with counsel that an objection by one is good for all defendants. That's fine with the plaintiffs. And we can reserve all objections besides form. That's also fine.

I'll also do little housekeeping. I'm going to go ahead and premark, I think, all the exhibits I'm going to use.

Exhibit 1 will be the doctor's report in the Perry case dated June 27th, 2024.

Exhibit 2 will be the doctor's supplemental report dated July 2nd, 2024.

Exhibit 3 will be the combined correspondence between counsel and the

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(Exhibit 7 was marked for identification.)

(Exhibit 8 was marked for identification.)

(Exhibit 9 was marked for identification.)

BY ATTORNEY IOLA:

Q And with that, Doctor, we'll get started. Thank you for indulging me.

You understand you're testifying today in the Perry case filed in South Carolina; correct?

A Yes.

Q Do you know the trial date of this case?

A Not offhand, no. I think I heard it's coming up soonish, but I don't know the exact date.

Q Okay. Have you been asked to make yourself available or to understand your availability for any particular range of days related to this trial?

A You know, it's possible. I mean, I think generally speaking, that's my understanding, is that, you know, I would have

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Page 10 1 to be present. I have an assistant who works 2 with my calendar. So probably somebody's talked 3 to her about, you know, the dates that I'm 4 around and available. 5 Q What does -- I understand there's a 6 litigation consulting part of your professional 7 time. I want to set that aside for a second. 8 Your day-to-day non-litigation-consulting 9 professional time, what does that look like? 10 A Well, I'm full-time at Hopkins. And 11 so it's a -- you know, depending upon the, you 12 know, the week, the weeks of the year, it 13 affects, you know, what I'm doing clinically. 14 So, like, you know, for the inpatient schedule, 15 you know, we have a schedule where we rotate 16 into, into different units. 17 You know, so one week I might be on 18 the pulmonary service, another I might be in the 19 oncology center, you know, another in an 20 intensive care setting. So depends on what the 21 schedule says. 22 And then on weeks when I'm not 23 physically in the hospital, you know, every 24 week, then I see patients in the outpatient 25 clinic. And then there's a mixture of, you	Page 12 1 in front of you. But I'm looking at your June 2 27th, 2024 report. And one of the first 3 paragraphs describes what you were asked to 4 determine, specifically the potential role, if 5 any, of various talcum powder products sold by 6 various manufacturers. 7 Do you see where I'm at on the first 8 page? 9 A I do. 10 Q Can you walk me through all the 11 people that have retained you in this case, to 12 the best of your knowledge? 13 A Rather than people, the companies? 14 Q Yeah. I was a bit colloquial in my 15 question there, for sure. Yes, the companies 16 that have hired you in this case. 17 A Okay. Yes. So I think -- so it's 18 Johnson & Johnson and Avon, Vi-Jon, Est e 19 Lauder, I think it's PTI Royston -- you know, to 20 the extent that they, you know, bottled the Gold 21 Bond and Ammens products -- and then IMI Fabi. 22 And I think that's it. I don't 23 remember whether Walmart -- because I know that 24 the J&J talcum powder products, I think, are 25 ones sold through Walmart. So I don't know if
Page 11 1 know, teaching, research, and administrative 2 things that fill the rest of the time. 3 Q Okay. And why would you have 4 occasion to be over in the oncology unit? 5 A Oh, well that's -- it's one of -- we 6 co-attend there with the oncologists. So the 7 pulmonary critical care service has a -- we have 8 a regular presence there. So we do, you know, 9 all the consultations on people with pulmonary 10 issues and then anyone who's critically ill. 11 Like, we don't have a separate ICU 12 for oncology patients. The oncology center is 13 itself ICU-capable. And so we're already there, 14 you know, for that. 15 Q Okay. That's that necessity of 16 interdisciplinary approach for the critical care 17 patients; right? 18 A Absolutely. 19 Q Okay. Do you know if Mr. Perry's 20 alive or dead? 21 A I don't have any information that 22 he's deceased. So last I was aware, he is 23 alive. 24 Q Okay. And for context here -- I'm 25 not going to show it to you; I know you have it	Page 13 1 I'm retained specifically by Walmart, but I 2 might be. 3 Q Okay. I was actually going to ask 4 you that because in that paragraph on the first 5 page of Exhibit 1 it says for the J&J products 6 you were asked to evaluate what role, if any, 7 they played for the J&J products that were 8 allegedly purchased at Walmart locations. 9 Is that to say you're only evaluating 10 the J&J baby powder that was allegedly purchased 11 at Walmart? Or you're evaluating all of the J&J 12 baby powders, regardless of whether they're 13 purchased at Walmart or someplace else? 14 A Well, I'd have to look to be 15 absolutely sure. But I think that was the task, 16 you know, was the first part, which was those 17 that were sold. 18 But I think that the industrial 19 hygiene reports cover -- if I remember right; 20 I'd have to look to be sure -- I think they 21 cover all the J&J. 22 Q Uh-huh. 23 A So, I mean, my opinion would probably 24 encompass, would encompass that as well. But I 25 don't think I was asked, necessarily, to

Page 14 1 consider all of it. 2 Q Okay. And we'll get into this in 3 more detail shortly. But I guess as a practical 4 matter, evaluating J&J products sold at Walmart 5 or all J&J products that Mr. Perry would have 6 encountered in this lifetime is kind of -- it's 7 an academic exercise because your opinion is 8 that the sum total of the potential exposures to 9 asbestos from the J&J baby powder did not 10 increase his risk, so any subset of that would 11 also not increase risk of meso; right? 12 A Yeah. That's fair to say. 13 Q Okay. Let's talk a favorite subject. 14 Let's talk money, quickly, and we'll get it out 15 of the way. 16 I've been provided certain invoices 17 that I've marked as Exhibit 5. We don't need to 18 go over those. But let me just ask: To the 19 best of your knowledge, is there any time that 20 you have spent on this case for any of the 21 companies that have retained you that has not 22 yet been billed, that is not reflected in the 23 invoices that I have? 24 A Oh, sure. Yeah, definitely. 25 Q How much. How much time?	Page 16 1 accounting for the gross amount of money billed 2 related to professional legal consulting, you 3 kind of separate them between asbestos and talc. 4 Is that fair? Or do you lump those together? 5 A Oh, no -- well, it's easier for me to 6 think about it in those two categories. 7 Q Sure. 8 A And the third category would be, you 9 know, cases that have nothing to do with either 10 one of us. 11 Q Absolutely. And let's operate in 12 those buckets. So for the year 2024 -- we're 13 about halfway through the year, somehow -- for 14 the asbestos work -- not the talc, but let's put 15 it in the first bucket, the asbestos work -- do 16 you have a sense of the total amount of money 17 billed? 18 A It would be an estimate that could be 19 not very accurate. I don't think it's, I don't 20 think so much. I think it might be -- I mean, 21 not so much compared to what you maybe read that 22 I testified about for other years. I think at 23 the end of the quarter, maybe \$50,000 or so. 24 Q Okay. How about for the talc work 25 for this year?
Page 15 1 A So -- and we're talking about my 2 personal time; right? 3 Q You -- 4 A Just to explain, because, like, the 5 invoices you have, they have, you know, they 6 have time of people other than me on the 7 invoices. So I don't have any estimate for 8 people other than me. But I'd say somewhere 9 around 25 or so hours that I've not billed yet. 10 Q Okay. And remind me your billing 11 rate for the materials reviewed/preparation 12 before deposition? 13 A Yeah, my personal rate is \$600, which 14 is what I get. And it gets billed at 725. 15 Q Okay. So approximately 25 hours 16 at -- well, I just did the math in my head at 17 the 600. That was about \$15,000. Does that 18 sound right? 19 A That sounds right, yeah. Yeah, that 20 sounds about right. 21 Q Okay. In terms of -- I had the 22 opportunity to read a couple depositions that 23 you've given in the past, so I'm trying to 24 borrow some of your language here. 25 My understanding is that in terms of	Page 17 1 A Yeah, that's, I would say, more on 2 the order of between 150- and 200,000. 3 Q Okay. And then for non-asbestos, 4 not-talc legal consulting, do you have anything 5 that fits that criteria for this year? 6 A Yeah. And probably, you know, less 7 than 50,000 for that category. 8 Q Okay. And for that last category the 9 non-asbestos, non-talc legal consulting work, 10 what are the subject matters that you're 11 consulting on then? 12 A All sorts of things. Like, you know, 13 some is medical malpractice. You know, some is 14 toxic tort cases that have to do with, you know, 15 mold and indoor dampness, chemicals, you know, 16 like, usually, like, inhalational exposures. 17 Q Okay. At the end of the day the 18 setting -- well, I guess even the medical 19 malpractice is going to be some sort of 20 evaluation of a pulmonary issue; is that fair? 21 A It's -- I'd say -- is not always 22 pulmonary, but it can be. It includes, like, 23 internal medicine issues -- 24 Q Okay. 25 A -- you know, so -- not this year, but

Page 18 1 I'm just thinking, for example, there was a case 2 I was involved in that involved, like, a low 3 sodium and the management of that, which isn't a 4 pulmonary; it's more a critical care or an 5 internal medicine issue. 6 Q Okay. For the -- again, this last 7 category, the non-asbestos, not-talc legal 8 consulting work that you've done this year, have 9 you been retained by any plaintiffs in those 10 cases? 11 A Oh, sure. Yeah. 12 Q In what kind of cases have you been 13 retained by plaintiffs? 14 A So, like, mold and indoor dampness 15 and then malpractice. 16 Q Okay. Is it accurate that you've 17 never been retained by a plaintiff in an 18 asbestos or talc case? 19 A That is correct. 20 Q Okay. To the best of your knowledge, 21 do you know if any Court has ever precluded your 22 testimony in whole or in part? 23 A In whole, I'm not aware of any. I 24 think in part, the Court that's relevant for 25 this current case I think has limited testimony	Page 20 1 years ago? 2 A No, none. It's the same. 3 Q Okay. Some basic questions for you. 4 You're not a pathologist, but you're -- so 5 you're not here to confirm or dispute whether or 6 not Mr. Perry was correctly diagnosed with a 7 pleural epithelial meso; correct? 8 A So not a pathologist. And, you know, 9 I would say the most I could do is affirm that 10 it makes sense, based on looking at the medical 11 records. Like if I saw something, for example, 12 where the treating clinician said "No, this is 13 in fact something else," you know, I would 14 acknowledge that and -- you know. 15 Q Okay. 16 A But I'm not the person to look under 17 the microscope and say "yes, indeed" or "no, 18 it's not." 19 Q Sure. And for the purpose of this 20 case, you did have an opportunity to review all 21 the medical records that were provided you; 22 correct? 23 A That's correct. 24 Q And do you agree that the course of 25 treatment and the course -- the clinical course
Page 19 1 in a couple of areas. I'm not sure I know, you 2 know, for sure the details of those. 3 And other than that, I don't think my 4 testimony's been excluded. I think there's -- 5 sometimes the judge will say that there's a word 6 that we're not allowed to say or something to 7 describe things. But I don't think that's the 8 same as limiting the testimony, per se. 9 Q That makes sense to me. My 10 understanding is the same as yours, that there 11 was an order from Judge Toal, who's the 12 presiding judge in this matter as well, in a 13 previous case that, at least in part, precluded 14 you from giving the opinion that a plaintiff's 15 mesothelioma was caused spontaneously. 16 Does that sound familiar to you? 17 A It does. 18 ATTORNEY COWAN: Form. 19 BY ATTORNEY IOLA: 20 Q Okay. As you sit here today, how, if 21 at all, have your opinions on the causation of 22 spontaneous mesotheliomas in general or as 23 applied to a specific person changed, either the 24 substance of the opinions or the methodology? 25 Have they changed at all since, let's say, two	Page 21 1 that Mr. Perry has undergone leading up to his 2 mesothelioma diagnosis into the present day is 3 consistent with someone who has pleural 4 mesothelioma? 5 A Yeah, I think all of that's true. 6 Q Okay. Do you agree that eventually 7 Mr. Perry will likely die from his mesothelioma? 8 A I think that's likely unless there's 9 some other intervening, you know, cause of 10 death. 11 Q Okay. Do you agree that mesothelioma 12 is an extremely painful way for patients to die? 13 A No, not necessarily. I think that -- 14 I think there was a different era in medicine 15 where lots of things were extremely painful. I 16 think that, you know, the palliative care 17 services and the attention that, you know, we 18 give in our cancer center, there's a big focus 19 literally on pain control and assessing it 20 regularly and trying to prevent it or manage it. 21 So no, I would hope not. 22 Q As I understand your answer -- 23 correct me if I'm wrong -- it's not that someone 24 in the end stages of mesothelioma is not 25 undergoing an immense amount of pain; it's that

Page 22 1 the pain management techniques have come a long 2 way. Right? 3 A Well, that was what my answer was. 4 But I don't -- I mean, if the issue, for 5 example, is that, you know, somebody has a 6 pleural effusion that's not manageable or, you 7 know, they develop an infection, you know, as a 8 consequence of maybe being immunocompromised or 9 something, that's not necessarily painful, 10 right. 11 Q Okay. 12 A There may be some other unpleasant 13 aspects of it. We're talking specifically about 14 pain. That doesn't have to be, you know, the 15 pathway towards the end. 16 Q Okay. My understanding -- again, 17 correct me if I'm wrong -- that the end stages 18 of mesothelioma, specifically pleural 19 mesothelioma, is basically someone suffocating 20 to death. Is that accurate? 21 A I think it depends case by case. I 22 mean, I think that -- you know, I think that 23 somebody can -- suffocating's sort of a lay 24 term. I think that you could say somebody's 25 having respiratory failure, for example. And	Page 24 1 always a time-and-place issue. But I think in 2 the United States, for example, over the past, 3 you know, several decades, I think that's been 4 the case. 5 Q Okay. Sometimes certain experts have 6 percentages that they like to assign to pleural 7 mesotheliomas in men caused by asbestos exposure 8 is X percentage; Y percentages are the remainder 9 that aren't caused by asbestos exposure. 10 Do you have numbers that you find 11 reliable for that purpose? 12 A So the issue, then, is, like, is the 13 attributable risk -- or the attributable risk 14 fraction would be, like, the epidemiology terms. 15 Q Right. 16 A And there aren't a lot of studies 17 calculated in the United States. Spirtas is a, 18 you know, 20-year-old study. But that had an 19 estimate. I think for men, for pleural, I think 20 it was 80 percent that were attributable to 21 asbestos exposure. For peritoneal meso it was a 22 lower percentage. And for women it was a 23 minority for both combined. 24 Q Okay. I know that those are Spirtas' 25 numbers. That's 1994, correct, that study?
Page 23 1 that's one possible, you know, sort of pathway. 2 But doesn't have to be. There's 3 other things that people with a malignancy, 4 including mesothelioma, can die from that isn't 5 just that pathway. 6 Q Okay. You agree that all of the 7 treatment that Mr. Perry has received in 8 relationship to his mesothelioma diagnosis has 9 been palliative in nature; correct? 10 A So, I guess it depends -- I mean, so 11 palliative, you know, in general has a broad 12 umbrella of what it does, but it's meant to 13 provide comfort. 14 You know, I do think I read at one 15 point, you know, that part of the goal was to 16 extend, extend life and extend the quality of 17 life. So I don't know that that's all 18 palliative care. I think, you know, if you're 19 using chemotherapy and/or radiation therapy, it 20 can have a palliative role, but it can also be 21 to try to extend the length of life. 22 Q Okay. Do you agree that the vast 23 majority of pleural mesotheliomas in men are 24 caused by asbestos exposure? 25 A So I think the majority -- and it's	Page 25 1 A That's correct. 2 Q Do you find that 80 percent number to 3 be more or less reliable for pleural 4 mesotheliomas in men born in North America in 5 the 20th century? 6 A I think so. I mean, I guess the -- 7 what I would wish for is that there be an 8 updated study; because as I understand the 9 trends, you know, the trend lines in the last 10 ten-plus years sort of showed a decline in men's 11 mesothelioma, pleural mesothelioma in 12 particular. It seems to correspond with the 13 reduction in the use of, you know, commercial 14 asbestos. 15 And so, you know, I think that 16 attributable fraction will come down. But I 17 don't have a number to assign to it. 18 Q Okay. And I appreciate you indulging 19 me on some of these general questions. I know 20 you've probably been through this before. But 21 it will expedite the process. 22 A That's fine. 23 Q Can you walk me through all of the 24 risk factors for an increased risk of 25 mesothelioma, the ones that you believe in?

Page 26 1 A Sure. And I guess we'll talk about 2 pleural mesothelioma? 3 Q Yeah, let's talk pleural. It's 4 easier that way. 5 A Sure. Yeah. So, you know, asbestos 6 in a sufficient dose is a risk factor. I think, 7 you know, other, other minerals have been 8 identified, like, you know, erionite and 9 balangeroite; that -- radiation; that -- there's 10 some information about inflammation or treatment 11 for tuberculosis that might be a risk factor. 12 And then, you know, I guess in a 13 general sense, other risk factors include 14 potentially having, you know, an inborn or 15 inherited genetic error that might increase the 16 risk or be determinative. And then time and 17 replication. So, you know, and age-related 18 effect from replication errors. 19 Q Okay. Let me try to break that down. 20 You said asbestos in sufficient dose can 21 increase risk of mesothelioma. Is that all 22 fiber types, all six regulated fiber types? 23 A So I'd say probably. I mean, it's 24 very hard to find studies on actinolite. I 25 mean, I understand that it's an amphibole and it	Page 28 1 A And then there's, you know, there's 2 others that are sort of coming, coming along. 3 Like there's -- and I don't remember the authors 4 of any of them off the top of my head. But 5 there's -- you know, in Central Mexico there's a 6 case report. I think there might be a case 7 series there also. 8 And then, you know, I read something 9 a little while ago that was talking about 10 erionite areas in the United States. So, for 11 example, I think like the, like the Upper, Upper 12 Midwest or kind of to the left of that -- you 13 know, like maybe Montana or some places where 14 there might be erionite found. 15 Q Okay. Besides the Turkish studies, 16 the series of Turkish studies of people exposed 17 to erionite, there's not a lot of epidemiology 18 on erionite; correct? 19 A That's right. 20 Q Have you seen the papers -- I think 21 they're in the last two or three years -- about 22 the Turkish villagers exposed to erionite that 23 evaluated the relative importance of genetic 24 factors versus the erionite exposure in certain 25 families that might have mesothelioma
Page 27 1 would make sense to me, you know, that it can 2 cause mesothelioma. I just think it's hard to 3 find studies. 4 And the same's true with 5 anthophyllite. I think there's, you know, not 6 as robust a literature as there is for the other 7 four, four fiber types. 8 Q Okay. The actinolite, we can draw 9 analogies to tremolite to understand potential 10 carcinogenicity because they're on the same 11 solid solution series; right? 12 A I don't know if I know the term 13 "solid solution series." But I think there is 14 some analogy, generally speaking, between the 15 fiber types. 16 Q Okay. For erionite, what studies do 17 you rely on that have erionite carcinogenicity, 18 just the ones that come to mind for you that 19 stand out as important? 20 A Yeah, I mean, like the Cappadocia 21 ones, you know, for the most part. I don't 22 remember each citation. I may have included 23 them, you know, in my literature considered. 24 But the Turkish ones, for the most part. 25 Q Okay.	Page 29 1 predisposition syndromes; right? Have you seen 2 those? 3 A Well, I think so. I mean, with 4 Carbone, I think that's, that's the group that 5 he started his investigation with, you know, was 6 that particular group because it was so 7 compelling and concentrated. 8 Q Okay. And the conclusion from 9 Carbone and the co-authors is that it's a 10 multivariable effect, where you have both the 11 genetic component and you have the toxicity 12 component of the environmental exposure to the 13 erionite; correct? 14 A I think in general, yeah, meaning 15 that each of those, each of those can play a 16 role in the risk of the cancer. 17 Q Right. Okay. Is there any evidence 18 that you rely on -- in the context of erionite 19 again -- that characterizes erionite as 20 asbestiform? 21 A I'd have to look back and see. I 22 thought that was true. But I don't -- you know, 23 if we're going to look at the articles and the 24 word's not there, I may be misremembering. But 25 I thought that was true.

Page 30 1 Q Let me ask it a different way, which 2 I think maybe is a little easier, which is: In 3 all the studies you've seen of erionite, the 4 concern and the characterization mineralogically 5 of the mineral particles being looked at is as 6 fibrous or non-fibrous; correct? 7 A Yeah; although I don't know about 8 whether there is non-fibrous erionite. I mean, 9 maybe there is. I just don't know that there 10 isn't. But I think the concern was that it was 11 a fiber. 12 Q Okay. And turning to balangeroite, 13 sort of the same issue: Have you seen any 14 studies that characterize the balangeroite as 15 asbestiform or non-asbestiform? 16 A Yeah; fibrous for sure. And 17 I just -- you know, I'd have to look to see if 18 the word "asbestiform" was used in the articles. 19 Q Okay. For both erionite and 20 balangeroite, the thing that is the same about 21 them is that these are fibrous respirable 22 mineral particles that have been shown to 23 increase risk of mesothelioma; correct? 24 A That's right. 25 Q Okay.	Page 32 1 Q Okay. You also mentioned the 2 genetics, errors. We'll get to that in due 3 course. Let me ask you about a few other 4 things. 5 Are you familiar with 6 winchite/richterite? 7 A I mean, I've seen like a -- I've seen 8 papers that talk about that. I'm not sure what 9 it is. Is it one of, like, the -- there's, 10 there's some of the names of the non-asbestiform 11 amphibole minerals. I don't know if that's one 12 of those. 13 Q I wouldn't use the word 14 "asbestiform." Just for context, where 15 winchite/richterite usually pops up is as two 16 types of nonregulated amphiboles that primarily 17 appear as a contaminant of vermiculite, 18 sometimes referred to as the Libby amphibole 19 mixture. Have you ever heard of that? 20 A Oh, yeah. For sure. 21 Q Okay. Do you have an opinion as to 22 whether or not Libby amphibole or 23 winchite/richterite specifically can increase 24 the risk of mesothelioma? 25 ATTORNEY COWAN: Form.
Page 31 1 A And actually, I just want to be 2 careful because your statement's fairly 3 definitive. I think with the balangeroite, it's 4 suspected. You know, I'm just sort of 5 summarizing, but I think that there's some 6 concern that there might be tremolite in the 7 mines or some other source of asbestos. And so, 8 you know, I think the state of the literature 9 now is that it might be carcinogenic. But I 10 think it's still an open question. 11 Q Okay. And feel free to -- whenever 12 you want to provide more context, that's fine, 13 Doctor. So thank you for doing that. 14 You mentioned -- by the way, 15 Mr. Perry, no evidence of exposure to erionite 16 or balangeroite; correct? 17 A Correct. 18 Q You also mentioned TB. I believe 19 this was kind of an old type of treatment for 20 tuberculosis many decades ago; correct? 21 A Yeah; plumbage, which isn't done 22 anymore. 23 Q Right. No evidence that Mr. Perry 24 had this treatment; correct? 25 A That's correct.	Page 33 1 THE WITNESS: I've heard that it can. 2 But I haven't really made a study of it. 3 So I don't -- you know, I don't know the 4 quality of the evidence. But I know 5 that -- you know, I've seen that some 6 folks say that it does. 7 BY ATTORNEY IOLA: 8 Q Okay. Are you familiar with 9 fluoro-edenite? 10 A Not super familiar. But I think it's 11 in my report as something that's on the list of 12 other minerals that may cause mesothelioma. 13 Q Okay. And would you put 14 fluoro-edenite as in the same bucket as the 15 balangeroite, in the sense that, not 16 particularly well-characterized but there is 17 some concern about a relationship between 18 exposure to these minerals and mesothelioma? 19 A Yes. 20 Q Okay. Are you familiar with carbon 21 nanotubes? 22 A A little bit. I mean, I've seen some 23 studies that have looked at those. So I have 24 some familiarity. 25 Q And as I understand it -- correct me

Page 34 1 if I'm wrong -- carbon nanotubes, sometimes 2 referred to as multi-walled carbon tubes, these 3 are synthetic. These are man-made 4 nanotechnology, basically; right? 5 A I understand they're man-made. I 6 don't know about the multi-walled part. That's 7 not familiar to me. But I've just heard them 8 called carbon nanotubes. 9 Q Okay. And there is concern in the 10 medical and scientific literature that these 11 carbon nanotubes, because they share the same -- 12 sometimes share the same shape and size as other 13 mineral particles that we know to cause 14 asbestos-related diseases, there's some concern 15 about people getting exposed to it and whether 16 they'll develop asbestos-related diseases; 17 right? 18 A Well, I think there has been concern. 19 Like, I don't know as a fact that there still 20 is. I mean, I haven't looked into it in a 21 while. But I remember at least one paper that 22 did not show a risk from it. So I don't know 23 the extent of the literature at the moment, 24 whether there's still a concern or not. 25 Q If you ever get curious, my PubMed	Page 36 1 stop there. 2 You've seen that; right? 3 A Yeah, I mean, there's the McDonald 4 papers, and there may be others as well. 5 Q Right. What do you think about that? 6 Do you -- are you a subscriber to the amphibole 7 hypothesis, meaning that it's really the 8 tremolite that's causing the diseases in the 9 Canadian miners and millers? Or do you believe 10 that chrysotile has a role too? 11 A Oh, so it -- yeah, I don't -- so I 12 don't know for sure. So I think those studies 13 were interesting and I think it certainly, you 14 know, pointed towards tremolite being an 15 important constituent that elevated the risk. 16 If you're asking do I think that it's 17 not possible for chrysotile asbestos to cause 18 mesothelioma, I don't subscribe to that. I 19 think in sufficient dose that it is possible. 20 Q Okay. So for the Canadian 21 chrysotile, the mixture of the chrysotile and 22 the low levels of tremolite, it's your opinion 23 that both of the asbestos fiber types would play 24 some role in increasing risk of disease in these 25 miners and millers in Canada, dependent on
Page 35 1 alerts every Saturday are full of carbon 2 nanotube papers. They seem to be doing a lot of 3 work on that. 4 Are you familiar with -- and I 5 realize this is kind of colloquial, but there's 6 something referred to as the "amphibole 7 hypothesis" as it refers to -- as it relates to 8 what's called "Canadian asbestos," the mixture 9 of chrysotile and low levels of tremolite. 10 Are you familiar with that? 11 A So, I mean, I think I've heard, you 12 know, the term "amphibole hypothesis" in a 13 couple of different contexts. But are we 14 talking about, like, the different mines in 15 asbestos where the miners and millers were 16 examined and there was, you know, one -- where 17 one mine seemed to have tremolite and the other 18 one seemed to not have tremolite and there was a 19 different risk? 20 Q I think that's pretty much exactly 21 what I'm getting at, the idea that it's not 22 really the chrysotile that's causing an 23 increased risk of asbestos-related disease in 24 the Canadian miners and millers, it's actually 25 the low levels of tremolite -- well, let me just	Page 37 1 whether or not they've been exposed to a 2 sufficient dose; is that fair? 3 A Well, not as a fact in those studies. 4 I mean, I don't know if they achieved a dose 5 that mattered. I'd have to look back, you know, 6 if it was chrysotile predominantly or chrysotile 7 only, if such a thing exists. 8 But I think within those studies, I 9 mean, I think what it showed was risk in those 10 that had tremolite exposure and not that risk in 11 the people who were either predominantly or only 12 exposed to chrysotile. 13 Q Okay. Have you seen any of that 14 mineralogical or geological analyses of either 15 the raw Canadian chrysotile or in fiber 16 digestions of people exposed to the same that 17 characterize the tremolite as asbestiform or 18 non-asbestiform? 19 A If it's part of that same series, I'm 20 sure I've seen it, but not recently enough to 21 recall the detail. 22 Q Okay. If all of the tremolite that 23 was found on fiber digestion in the Canadian 24 miners and millers was classified as 25 non-asbestiform cleavage fragments, does it

Page 38 1 still play a role in causing disease? 2 A So, I guess, you know, fiber 3 digestions are one thing. You know, whether 4 somebody was exposed to, you know, asbestiform 5 tremolite is another issue. I mean, whether 6 it's found in the digestion or not isn't 7 necessarily the same as the fact of whether or 8 not they inhaled it or were exposed to it. 9 If we're talking about cleavage 10 fragments, I think that's a completely different 11 area. I don't know what the role of cleavage 12 fragments is in disease. And I don't really 13 have an opinion about, you know, cleavage 14 fragments and their potential for disease. 15 For me, I've kind of left off with 16 the NIOSH roadmap, which said, you know, it's an 17 area of interest that should be studied. But 18 I'm just not aware that that investigation has 19 come to fruition to say that cleavage fragments 20 of any sort are a risk factor for mesothelioma. 21 Q That's a great point. Let me put it 22 a different way. Maybe it's the opposite way of 23 how you said it, which is: You do not share the 24 opinion that some other people believe, that 25 cleavage fragments have been shown to	Page 40 1 of it -- some of the factors that are important 2 for mineral particles and mesothelioma -- let me 3 just start with the first one. 4 The first one's going to be shape and 5 size; right? Is it respirable? Is it 6 sufficiently long to cause disease? Is it too 7 wide to be inhaled? These are things that 8 you're concerned about as a pulmonologist; 9 right? 10 A Sure. It has to get into the lungs. 11 Q Okay. There are some people that 12 believe that only so-called long asbestos 13 fibers, greater than 5 microns, can cause any 14 asbestos-related diseases. Do you agree or 15 disagree with that or have no opinion at all? 16 A Well, I think the evidence supports 17 that. I mean, you know, going back to some of 18 the experimental stuff with Stanton and so 19 forth. 20 I think for the human epidemiology, I 21 think it's really -- I haven't found anything 22 convincing about short fibers -- and whatever 23 that is. Short, you know, may be less than 24 5 microns in length. 25 But, you know, I think one of the
Page 39 1 definitively not cause disease? It's your 2 opinion that more research is needed; is that 3 fair? 4 A That is fair. 5 Q Okay. Do you have an opinion about 6 what are the things or the factors about 7 asbestos fibers specifically that make them such 8 a potent cause of mesothelioma in human beings? 9 A Not in detail. I mean, I think 10 that's somebody else's field. You know, I 11 think -- 12 Q Okay. 13 A -- other than, like, for example, 14 persistence of the fibers. You know, I think it 15 seems important that for the ones that are the 16 amphibole types that we're talking about, the 17 regulated ones, that they persist and persist 18 long enough to have an effect. 19 But, you know, and I know there's 20 different theories about, you know, the iron 21 content and other things. But that's not really 22 my field. 23 Q Okay. From your perspective as -- 24 and I don't mean to suggest this is all of what 25 you do, but certainly pulmonology is a big part	Page 41 1 issues with the epidemiology studies is that 2 when the fibers are indeed measured, they're 3 measured using, typically, the -- you know, the 4 counting rules that include looking at fibers 5 that are 5 microns and longer. 6 So I just -- I'm not aware of a body 7 of evidence that's shown risk in humans, you 8 know, from shorter fibers, which aren't 9 typically counted, you know, by NIOSH 10 methodology. 11 Q And that's one of the limitations of 12 looking back at these epidemiology studies to 13 understand the role of fiber sizes. If you're 14 not counting -- if it's there, if you're not 15 counting fibers less than 5 microns, you can't 16 figure out what role, if any, they contributed 17 to the risk; right? 18 A Not from the studies; that's right. 19 Q Right. Have you seen the early 2000 20 Suzuki studies -- and there's a few other 21 assorted studies as well; I think Stayner is 22 one -- that show for mesothelioma the 23 predominant fiber type found in the pleura is 24 chrysotile and the predominant fiber size is 25 short-fiber chrysotile?

Page 42 1 You've seen the studies; right? 2 A I have, yes. 3 Q All right. What I'd like to do now 4 is just kind of start walking through your 5 report, sir. I'm looking at the June 27th, 2024 6 Perry report, and I'm looking at page 2. And 7 I'm just going to start there. 8 You have a section here that's 9 Background and Employment History for Mr. Perry; 10 correct? 11 A That's right. 12 Q And you note that Mr. Perry's father 13 was an aviation mechanic and inspector. Let me 14 pause there. You've seen no evidence that 15 Mr. Perry had any take-home exposures to 16 asbestos or other fibrous mineral particles of 17 concern related to Mr. Perry's father's work; 18 correct? 19 A That's correct. 20 Q You also note that at the time of 21 Mr. Perry's deposition his father was 78 years 22 old, had late-stage prostate cancer -- let me 23 pause there. 24 Is prostate cancer one of the BAP1 or 25 other germline mutation diseases associated --	Page 44 1 So it's one that's been found in 2 association. It's not that classic, you know, 3 two or three where, you know, the report 4 started, you know, with those few, you know, 5 rare types of tumors. 6 Q Those classic two or three that you 7 mentioned -- and correct me if I'm wrong -- 8 would be some combination of renal cell 9 carcinoma, the ocular tumors, as well as 10 mesothelioma; right? 11 A Yeah; and specifically uveal melanoma 12 was the ocular. 13 Q Right. Thank you. I regurgitated my 14 layman recollection of it. So thank you for 15 that. 16 All right. Let's go back up. And 17 let me just ask the question instead of beating 18 around it, which is to say: It's your opinion 19 that Mr. Perry could possibly have some germline 20 mutation that may have caused his mesothelioma. 21 But because he's not had the full genetic workup 22 and profile, you don't -- you're not able to say 23 to a reasonable degree of scientific certainty 24 that he does have BAP1 or any other specific 25 germline mutation as we sit here today; is that
Page 43 1 well, I asked a terrible question. Let me start 2 again. 3 Is prostate cancer one of the 4 BAP1-related diseases that you look for in 5 someone who is also diagnosed with mesothelioma? 6 A Let me get you a better answer than 7 just off the top of my head. 8 Q Sure. Yeah, take your time, always. 9 A So I'd say yes. And I'll just 10 qualify it as recognizing that it's not one of 11 the classic initial ones, you know, from the 12 original investigators who looked at it, who are 13 focused on, you know, uveal melanoma and then 14 mesothelioma. But, you know -- and if it helps, 15 I'll just point you to where I'm looking -- 16 Q Sure. 17 A -- is page 39 and 40 of my report. I 18 have a list of -- I'll wait for you to get 19 there. 20 Q I am there, sir, thank you. Please. 21 A So the paragraph that ends at the 22 bottom of page 39, I've listed out tumors that 23 have been found in association with BAP1 24 mutation. And so -- and the prostate cancer's 25 on the next page, on page 40.	Page 45 1 accurate? 2 A It is. I mean, I think the best 3 estimate that I've seen is about 12 percent or 4 so of people with mesothelioma do harbor some 5 type of, you know, pathogenic mutation. But 6 absent testing, I can't say that he does or 7 likely does have one of those. 8 Q Okay. I did notice in the medical 9 records of Mr. Perry and his clinician's 10 investigation of the tumor itself, they noted 11 that the BAP1 was still intact. But for our 12 purposes here, that's kind of irrelevant because 13 that would be a somatic mutation not a germline 14 mutation because we're looking at tumor; right? 15 A Oh, no, it's actually really relevant 16 because it rules out BAP1 as a germline mutation 17 specifically. 18 Q Okay. 19 A So if he had a deletion, it could be 20 just a somatic deletion or it could come from 21 the inherited, you know, gene. But if he has it 22 retained in the tumor, then he can't have a 23 germline mutation in that part. 24 Q Okay. Do you see the medical records 25 that noted that BAP1 was still intact in the

Page 46 1 tumor? 2 A I did. 3 Q Okay. So that means, fundamentally, 4 Mr. Perry does not have a BAP1 germline 5 mutation, but he could possibly have another 6 unspecified germline mutation that could play a 7 role in the development of mesothelioma; is that 8 accurate? 9 A Absolutely. 10 Q Okay. All right. I know -- again, 11 I'm going to page 3 now. You note in 12 Mr. Perry's past medical history, one of the 13 things that he had had was a colectomy due to 14 some chronic inflammation from the 15 diverticulitis; right? 16 A That's right. 17 Q You don't have an opinion that the 18 inflammation associated with the diverticulitis 19 played any role in causing his mesothelioma; 20 right? 21 A I don't believe it did. 22 Q Okay. Going down to page 4 of your 23 report and employment history -- and this is 24 Mr. Perry's employment history; correct? 25 A That's right.	Page 48 1 Q Okay. So let me ask -- I'll ask it a 2 slightly different way, which is: If Mr. Perry 3 has exposure in 2017 to asbestos, he gets 4 diagnosed a couple years later. Do you have an 5 opinion one way or another whether or not that 6 would have contributed to tumor formation, given 7 the proximity in time? 8 A I don't see how it could have. And 9 it wouldn't -- it would be inconsistent with the 10 literature that, you know, that I've looked at. 11 Q Okay. So if I'm understanding your 12 opinion correctly -- obviously, correct me if 13 I'm wrong -- the exposures that contribute to 14 mesothelioma risk would need to be at least 20 15 years before the diagnosis of the disease or the 16 formation of the tumor; right? 17 A That's right. 18 Q Okay. You have a paragraph -- well, 19 it's really a long sentence here -- in regards 20 to the Social Security records of Mr. Perry. 21 Let me ask just a general question about that. 22 You've seen no evidence of any 23 contributing asbestos exposure from any of these 24 jobs reflected on the Social Security records; 25 is that accurate?
Page 47 1 Q You noted that Mr. Perry and a sister 2 walked beans and corn as a summer job in their 3 rural farming community. Let me pause there. 4 Do you have any opinion as you sit 5 here today that Mr. Perry would have had any 6 exposures to anything environmentally while 7 growing up that would have increased his risk of 8 mesothelioma? 9 A I mean, I have no evidence of that. 10 Q Okay. You note that after moving to 11 South Carolina, Mr. Perry worked for Hilton from 12 2000 to 2017. And I think you note later on in 13 the report that Mr. Perry reported some 14 potential exposures to asbestos associated with 15 his work for Hilton; is that right? 16 A That's right. 17 Q How close in time -- well, I could 18 ask it one of two ways, so I guess I'll ask it 19 both ways. How close in time or how far away in 20 time does an asbestos exposure need to be from 21 the time of tumor formation to actually 22 contribute to tumor risk? 23 A So, I mean, if we're talking about 24 latency, I think 20, 20 years is typical, you 25 know, is a minimum.	Page 49 1 A I'm sure it is. I'm just -- I'd have 2 to crosscheck to be sure because I think for the 3 Holiday Inn, Holiday Inn comes from -- let's 4 see -- yeah, his testimony. And then -- that's 5 right. 6 And again, I think you can tell what 7 I've intended to do is, where I have citations 8 for the Social Security Administration and I 9 list them -- 10 Q Yeah. 11 A -- and then say, you know, not 12 specified. And so that's a placeholder for me 13 which is, he didn't say so and I don't have any 14 other information either. 15 Q Okay. No, that is very helpful. 16 And if I look at the work history 17 chart on page 5, going forward a few pages, you 18 note, you know, some claimed asbestos exposure 19 to drywall and joint compound. Let's see. 20 ATTORNEY IOLA: I guess my gardeners 21 are here at a great time. Could we 22 actually maybe just go off the record for 23 ten minutes, see if they leave. 24 THE WITNESS: That's okay with me. 25 (Discussion held off the record.)

Page 50 1 (Recess.) 2 BY ATTORNEY IOLA: 3 Q Doctor, we are back after a short 4 brake. Thank you for giving me a little time 5 there. 6 To go back to Mr. Perry's social and 7 occupational history, let me see if I can 8 streamline this a little bit. Are there any 9 exposures to asbestos that Mr. Perry had either 10 occupationally, para-occupationally, 11 environmentally, or other that increased his 12 risk for mesothelioma, that you saw from your 13 review? 14 A I'd say I only saw one that was 15 possible, which is just what, you know, he 16 himself, you know, mentioned, was some potential 17 asbestos exposure when he was working at the 18 hotels. 19 Q Okay. And that would be -- let's 20 see. To orient us in time, at the hotels would 21 be -- this is the '85 to '93 at the Holiday Inn, 22 or is this later on in time at the Hiltons in 23 the 2000s, 2010s? 24 A Well, it would include that. And 25 then I think -- you know, I think,	Page 52 1 And I will say too -- I mean, I know 2 it's not my job to do it and we have to live 3 with what people testify. But I do find that, 4 you know, six dozen brake jobs on two cars in a 5 very small amount of time doesn't seem credible 6 to me. It just doesn't make any sense -- 7 Q Uh-huh. 8 A -- you know, as somebody who has 9 owned cars and worked on cars that -- you know, 10 unless it's a drag racer or something that he's 11 taking to the track, it doesn't seem conceivable 12 that that's a good estimate. 13 But even if it is, even assuming 14 that's the fact, it's still -- I still don't 15 see, you know, enough evidence that there is an 16 exposure that matters. 17 Q Okay. Have you seen -- to piggyback 18 off that, have you seen the EPA's part 1 risk 19 assessment for chrysotile asbestos related to 20 the Toxic Substances Control Act? Have you seen 21 that? It's from like from a year or two ago. 22 A I think I know of it, but I haven't 23 read it. 24 Q Okay. Then I'll leave it alone. 25 The next sections are the summary of
Page 51 1 theoretically, the part, you know, that's 2 outside that 20-year window that we talked 3 about. So not the -- you know, not total of all 4 those, you know, dates that he's mentioned but 5 just the ones that are, you know, long enough to 6 satisfy a latency consideration. 7 Q Okay. So basically the asbestos 8 exposures of potential concern to you are the 9 hotel-related work more than 25 years before his 10 diagnosis of mesothelioma; is that right? 11 ATTORNEY COWAN: Form. 12 THE WITNESS: More than 20. 13 BY ATTORNEY IOLA: 14 Q More than 20. Okay. Sorry. Okay. 15 Well, that streamlines it. 16 There was a mention, again, just to 17 be extra careful by me, on page 11 of your 18 report you note that Mr. Perry believed he was 19 exposed to asbestos as a bystander to his 20 family's brake work on family vehicles. 21 Is it your opinion that that would 22 not have increased his risk of mesothelioma or 23 contributed to cause his meso? 24 A Yeah. And I don't see enough 25 information to suggest a risk.	Page 53 1 Mr. Perry's use and exposure to talcum powder 2 products; correct? 3 A That's right. 4 Q Is it accurate to say that it's your 5 opinion that Mr. Perry did not have any 6 exposures to asbestos from any of the talcum 7 powder products that would have caused or 8 contributed to cause or increased his risk of 9 mesothelioma? 10 A No. I think -- I mean, it's an 11 unknown to me. I mean, I allow for the 12 possibility that he might have. It's also 13 possible that he had not. 14 Q Okay. And that kind of goes to the 15 secondary question. The primary question for me 16 is: Even assuming that Mr. Perry did have some 17 exposure to asbestos from some talcum powder 18 products, it would still be your opinion that 19 those did not contribute to increase his risk of 20 mesothelioma; correct? 21 A That is correct. 22 Q Okay. So you're allowing for the 23 possibility that Mr. Perry may have had some 24 exposures to asbestos at unspecified levels, 25 unspecified amount of time, from certain talcum

Page 54 1 powder products, but the actual magnitude of 2 that is kind of irrelevant to your risk 3 assessment because talcum powder with asbestos 4 doesn't cause meso; right? 5 ATTORNEY COWAN: Form. 6 THE WITNESS: Yeah. Although the 7 magnitude's relevant in the sense that I 8 think it's not a, not a magnitude that 9 rises to the level of concern. 10 BY ATTORNEY IOLA: 11 Q Okay. For each -- I'm going to try 12 to take these in order. For your assessment of 13 Mr. Perry's potential exposures to asbestos from 14 Johnson's baby powder product, I know you 15 reviewed -- you reviewed plaintiff expert 16 reports; correct? 17 A That's correct. 18 Q You reviewed the defense expert 19 reports in this case -- at least -- looks to me 20 like most of them if not all of them; right? 21 A That's correct. 22 Q Were you provided any other -- and 23 I'm setting aside deposition transcripts, the 24 pleadings, the medical records; let's set those 25 aside. And set aside the plaintiff expert	Page 56 1 something I possess; and it's not something I 2 keep track of. 3 Q Okay. And I know -- I think I saw 4 this in the previous depositions. You've been 5 asked questions similar to this before by other 6 plaintiff lawyers. You know, have you reviewed 7 internal testing of talc for asbestos? You 8 recall that; right? 9 A Oh, sure. 10 Q Is there a reason why today you still 11 have not reviewed any of the testing of talc for 12 the presence of asbestos that might be internal 13 to some of these companies? 14 A It's not part of my field. You know, 15 I mean, I'm a physician and an epidemiologist. 16 So I -- you know, whatever -- and "internal 17 documents," I'm not sure if it's a term. But I 18 think what we're talking about is, you know, 19 e-mails and memos and things of that sort. 20 You know, I've tried to rely for the 21 most part on, you know, for the most part, on 22 peer-reviewed published literature for, you 23 know, government reports, other statements of 24 that sort, you know, whether they're 25 peer-reviewed or not.
Page 55 1 reports; set aside the defense expert reports. 2 What other materials did you 3 read/review for this case specific to Johnson & 4 Johnson or Johnson & Johnson Baby Powder, if 5 any? 6 A Yeah; nothing else. 7 Q By way of example, let me just give a 8 little context. Dr. Haber, in the Perry case, 9 he keeps what he calls Exhibit B and C. Exhibit 10 B, I believe, is basically a listing of all the 11 internal company documents he's reviewed over 12 time. Exhibit C is the published, 13 peer-reviewed, available literature about 14 asbestos. 15 Do you keep -- I know you keep, 16 effectively, a reference list from the publicly 17 available literature vis- -vis your citations in 18 your report; right? 19 A That's correct. 20 Q Do you keep a list, like Dr. Haber, 21 of internal company documents typically related 22 to testing of asbestos in talc? Is that 23 something you review? Is that something you 24 keep track of? 25 A It's not something I review; it's not	Page 57 1 But it doesn't, it doesn't -- it's 2 not part of my process; right? Like, if I 3 undertake a meta-analysis, I don't go try to 4 find, you know, memos from people. It just 5 doesn't fit into my process. 6 Q Okay. Let me shift our terrain a 7 little bit and see if I can ask it in this 8 context. 9 You mentioned working in mold cases. 10 I think you said you do some of that work for 11 plaintiffs; right? 12 A That's correct. 13 Q In the mold cases, as part of your 14 risk assessment, do you have to assess whether 15 or not there's actually mold present? 16 A No. I mean -- and I'll just -- I 17 mean, I'll give you an example. Like, people 18 will do mold reports; right? I mean, there are 19 companies that will go out and do that. But, 20 you know, based on my own work in the field and 21 also epidemiology, those reports don't 22 contribute anything meaningful. 23 I mean, if someone gives one of them 24 to me, I'll acknowledge it. But for human 25 health, I don't need that information.

Page 58 1 Q Okay. Because it -- let me see if 2 I'm getting this right. Because the 3 peer-reviewed and publicly available literature 4 inherently has in context the assessment of 5 whether or not the substance being analyzed has 6 the toxin that you're looking for, that's just 7 part of -- that's part of the assessment that's 8 being done? That's not something you spend time 9 thinking about; right? 10 A Well, it's -- I don't know if it's 11 different. But it's in addition; right? So 12 from an epidemiology standpoint mold -- since 13 we're talking about mold, mold is very hard to 14 study because it's a, a life-form that goes 15 through many stages. 16 And so, you know, it's not really 17 clear which indicator of mold is a valid one for 18 assessing health risk -- whether it's the 19 spores, whether it's just a PCR test, you know, 20 and so forth. 21 But from epidemiology studies, what 22 works very well is a participant or a patient 23 report of visible mold. That's been shown to be 24 a valid indicator. And a musty smell, for 25 example, is actually very good because there's	Page 60 1 talc-containing asbestos; is that right? 2 A Yeah. I think I've phrased it a 3 little differently, just to be, you know, within 4 my field. I said that the epidemiologic 5 evidence does not support that there's a risk 6 from, you know, perineal applications of talcum 7 powder products and risk of ovarian cancer. 8 Q Okay. Do you agree that the link 9 between asbestos exposure and ovarian cancer has 10 been established in the medical and scientific 11 literature? 12 A I don't, no. And I think, you know, 13 despite the fact there's an IARC monograph, I 14 think that there are reasonable, you know, 15 considerations for why that may have been a 16 premature conclusion. But I allow for the fact 17 that it might. 18 It looks like, if you look at some of 19 the old historical studies from World War II era 20 and after, you know, if it is a cause of ovarian 21 cancer, it's at a very heavy dose of, probably, 22 commercial amphiboles. 23 Q The -- I have seen in some of the 24 ovarian epidemiology that one of the confounding 25 variables that's listed is the presence of
Page 59 1 VOCs that your nose detects. 2 And so for the state of -- even 3 though there's people who publish from, you 4 know, mold tests, they're really not valid for 5 assessing the effect on human health. 6 And just to go further, you know, 7 even when people are worried about mold, it's 8 usually not just mold. It's the indoor 9 dampness. So there's bacteria; there's viruses; 10 there's deteriorating wallboard which is, you 11 know, giving off VOCs. 12 So it's much more complicated than 13 just simply somebody doing a swipe, bringing it 14 back to the lab and saying "Oh, yeah, I found 15 this common mold inside your home." It's 16 practically meaningless. 17 Q Okay. Okay. Not exactly related to 18 what you said, but for some reason it popped 19 into my head. You testify in some of the 20 ovarian cancer talc cases; correct? 21 A That's correct. 22 Q And I take it from who's retained you 23 in those cases -- I haven't seen your testimony, 24 but I'm assuming it's your opinion that ovarian 25 cancer is not caused by either talc itself or	Page 61 1 asbestos in talc before the CTFA adopted the 2 J4-1 method in 1976. 3 Have you seen statements like that in 4 some of the epidemiology? 5 A Well, I've seen it. But it's usually 6 followed up too with then people -- and I think 7 what is it, 1976, of something that people are 8 talking about? 9 Q Yes, sir. 10 A So, yeah. But then some of the 11 epidemiology studies have considered that, and 12 they've looked at the risk pre/post 1976. And 13 there's no difference. So I haven't seen a 14 study that sort of affirmed that that even 15 matters, you know, that concept. 16 Q Okay. Have you seen the recent -- I 17 think it was released in the last three or four 18 weeks -- the NIH -- well, let me phrase it 19 differently -- the study done by certain 20 researchers at the NIH that was just published 21 assessing the risk of ovarian cancer from 22 perineal exposure to talc. I assume you've seen 23 that? 24 A I've seen it. And I'm just saying 25 this to be polite: I answered questions for

Page 62 1 about three hours about that study, I think a 2 couple weeks ago. So I can save you a lot of 3 time -- 4 Q That's all I need to know. 5 A Yeah, I can save you a lot of time if 6 you just want to read that. 7 Q No, no. That actually does save me a 8 lot of time. And really, I was just curious if 9 you've seen it. But that does help. Thank you. 10 A Yeah. 11 Q Going to the next section in your 12 report about Avon -- and just so you know, I'm 13 going to ask this for each set of talc 14 defendants or each talc defendant. Aside from 15 the materials that you reviewed reflected in the 16 plaintiff's expert reports, the defense expert 17 reports, and what I would call the case-specific 18 materials related to Mr. Perry -- the 19 depositions, the medical records, et cetera -- 20 have you reviewed any other documents 21 specifically related to Avon and Avon talcum 22 powder products? 23 A No. 24 Q Okay. Would that answer be true -- 25 would you give the same answer in relationship	Page 64 1 know, mine source link to each product that he's 2 claiming, you know, is an issue here. 3 Q There are a lot of different lawyers, 4 but I'm not that type of lawyer who's going to 5 waste our time going through that. I think your 6 answer is sufficient and points me in the right 7 direction. 8 Let me keep going down. 9 On page 25 of your June report, 10 towards the bottom, you begin a section titled 11 Past Medical History. Let me ask a global 12 question here. 13 Based on your review of the medical 14 records for Mr. Perry before his mesothelioma 15 diagnosis, were any of these -- were any of 16 these medical conditions life-threatening, 17 expected to reduce his life expectancy at that 18 time of diagnosis, not related to meso? 19 A I'd say the only one potentially 20 would be, you know, the fact that he has 21 coronary artery calcifications, which is an 22 indication of coronary artery disease. And so 23 that has the potential to limit his life 24 expectancy. 25 Q Okay. To the best of your
Page 63 1 to each talc defendant that you've been retained 2 by in this case? 3 A Yes. 4 Q Okay. That will definitely make this 5 go quicker. 6 For the -- do you have any knowledge 7 of the particular mine or mines, talc mines, 8 that were used for any of the talcum powder 9 products that Mr. Perry used at any particular 10 time? 11 A I was going to say yes. But then 12 when you finished it with Mr. Perry, I don't 13 know for a fact, you know, which mines were 14 linked. But what I rely on -- 15 Q Sure. 16 A -- is, like, the mineralogists, for 17 example -- so like Mr. Segrave, for example. 18 Q Right. 19 A So I may have pulled some of that 20 into my report. But what I rely on is what he's 21 looked at. And then some of the industrial 22 hygiene reports I think also pull that in. 23 Q Okay. 24 A I could look up what they say. But I 25 haven't, you know, memorized each and every, you	Page 65 1 recollection, was he on any medications related 2 to the coronary artery disease? 3 A I didn't, I didn't track them. 4 Q Okay. If -- let me ask it this way. 5 Sometimes in the medical records they'll refer 6 to it as -- a medical condition as controlled or 7 uncontrolled by medication. 8 Did you see any indication that the 9 coronary artery disease was uncontrolled, not 10 being treated with medication? 11 A I didn't see that. 12 Q Okay. In the next little section for 13 Past Surgical and Procedural History, towards 14 the bottom of that section, on page 28, there's 15 a mention of testicular cancer, 1990. Do you 16 see that? 17 A Yes. 18 Q You've seen -- well, let me ask it 19 this way. Have you seen any evidence that -- 20 besides this one notation in the medical record 21 of testicular cancer, have you seen any other 22 mention in any other documents related to this 23 case that Mr. Perry actually had testicular 24 cancer? 25 A I did not get another record that

Page 66 1 showed that. 2 Q Okay. If he had testicular cancer 3 and he's still alive nearly -- well, I guess, 4 more than 30 years later, is your expectation 5 that the testicular cancer, if malignant, was 6 treated, I guess? 7 A And I would go further and say cured. 8 It sounds like, as you're saying, if it's true 9 that he had testicular cancer, he had an 10 orchiectomy, which would be a surgical removal 11 of the tumor. And it sounds like it would have 12 been a resection for cure. 13 Q Okay. You haven't seen any evidence 14 that Mr. Perry had any radiation treatment for 15 any condition before his mesothelioma; correct? 16 A Yeah. Only, only following the 17 diagnosis. 18 Q Right. Okay. You have a section 19 here, as we keep going, page 29 and 30, of the 20 family history of, I'll call it, disease and 21 cancer. I guess, if there are any cancers on 22 here that might tend to show a propensity for a 23 germline mutation that could also cause 24 mesothelioma, the cancers that are of specific 25 interest are the ones that you and I already	Page 68 1 or common diseases, in the context of the 2 coronary artery disease; right? 3 A I... 4 Q Let me ask a different question. Bad 5 question. Bad question. I look at the face, 6 and that tells me all I need to know, you know. 7 Breast cancer, prostate cancer, lung 8 cancer, and ovarian cancer, or uterine cancer, 9 these are all fairly common cancers; right? 10 A I'd say all but ovarian. I mean, 11 ovarian is usually discussed as a rare cancer. 12 Q Okay. And the coronary artery 13 disease, especially in people over 60, pretty 14 common; right? 15 A It is common. 16 Q Okay. I note that, from the 17 records -- and I saw this note as well -- the 18 reference to a mesothelioma in a paternal 19 grandfather. Is that fair to say you've seen 20 the other record or evidence to suggest that the 21 paternal grandfather did have mesothelioma, 22 besides this one medical record? Is that 23 accurate? 24 A That's correct. This is the only 25 one.
Page 67 1 went over that are listed in your report; 2 correct? 3 A Well, that wouldn't be complete; 4 right? So we talked just about a BCRA mutation, 5 and then I had a list of cancer associated with 6 that. But if you look at -- I'm sorry, not 7 BRCA, BAP1. I misspoke. We talked about BAP1. 8 But, I guess, BRCA genes, for 9 example, you know, might link to, you know, 10 breast and ovarian cancer in his mom. And, you 11 know, the BRCA gene defect has been linked to 12 mesothelioma as well. 13 So sort of cancer by cancer, there 14 could be ones that point towards other 15 syndromes. You know, colon cancer, for example, 16 is listed here. There are various genes that, 17 you know, are linked to colon cancer. 18 So, yeah, just be clear, what we 19 talked about before was just BAP1. 20 Q Okay. Just looking at the list of 21 the diseases here that you list from the medical 22 records -- heart disease, ovarian cancer, breast 23 cancer, prostate cancer, lung cancer -- these 24 are all pretty common cancers; right? 25 Well, they're either common cancers	Page 69 1 Q Okay. All right. Going down to 2 page 32 of your report, in the section entitled 3 Differences Between Asbestos and Talc, you have 4 a -- the first sentence under the Asbestos 5 section says that: Asbestos is a term that is 6 used to describe several naturally occurring 7 silicate mineral species when they are present 8 in a fibrous form. 9 Do you see that? 10 A I do. 11 Q And when you were writing this 12 report, is it fair to say that that definition 13 of asbestos -- the fibrous variety of certain 14 silicate minerals -- is a definition of asbestos 15 that you've seen many times in different medical 16 articles, textbooks, peer-reviewed journals? 17 You've seen it numerous times; correct? 18 A Well, something similar. I mean, I 19 literally took this from a monograph from the 20 Institute of Medicine. 21 Q Right. 22 A I just thought that was a good place 23 to describe it from like a -- you know, like, 24 what medical doctors and scientists would be 25 interested in, as opposed to, like, what a

Page 70 1 mineralogist would say. 2 Q Right. And in that first sentence, 3 the word "asbestiform" does not appear; correct? 4 A That's correct. 5 Q In the next sentence, in all 6 fairness, you say "fibrous asbestos," and then 7 in brackets "known as asbestiform"; right? 8 A That's right. 9 Q So from your perspective as a medical 10 doctor, "asbestiform" and "fibrous," they're 11 interchangeable. These are symptoms; right? 12 ATTORNEY COWAN: Form. 13 THE WITNESS: No. No, they're not. 14 I mean, you can have something that's 15 fibrous that's not asbestiform. 16 BY ATTORNEY IOLA: 17 Q Okay. What definition of asbestos, 18 from a medical perspective, says that in order 19 for asbestos to be asbestos, it needs to be 20 asbestiform and not just fibrous? 21 A So I'm not sure I even understand 22 that. 23 Q It might be a bad question. Let me 24 try again. 25 Are you aware in any medical	Page 72 1 there's an evidence base to support that. 2 If there's something that's otherwise 3 the same mineral but it's too fat to be inhaled, 4 you know, then I don't think it poses a risk. 5 You know, I don't know if you need a study for 6 that, if it's not respirable. 7 So, yeah, I think there's plenty of 8 opportunities for something that's not 9 asbestiform to either have an unknown evidence 10 base or just not make sense that it could cause 11 harm. 12 Q Do you have an understanding that 13 there's some people -- usually a mineralogist or 14 a geologist -- you've probably seen this in 15 Mr. Segrave's report or Dr. Sanchez's report -- 16 that there can be an overlap in dimensions 17 between non-asbestiform cleavage fragments and 18 asbestiform amphiboles? Have you seen that? 19 A So non-asbestiform cleavage fragments 20 and asbestiform fibers? 21 Q Yeah; that have the same -- they can 22 have an overlap of size and shape, meaning -- 23 let me just give you an example -- that you can 24 have a structure is that's 8 microns long by 25 .25 microns wide -- that's a 40-to-1 aspect
Page 71 1 textbooks, medical journals, articles, that kind 2 of thing, where any medical doctor writes that 3 in order for a mineral particle to be asbestos, 4 it has to be one of these silicate minerals and 5 it has to be asbestiform; something more than 6 fibrous. Have you ever seen that? 7 ATTORNEY COWAN: Form. 8 THE WITNESS: Oh, I don't know. I 9 mean, I'm linking together a variety of 10 things, including just that asbestiform 11 seems to have a definition; right? 12 There's a certain, you know, dimension and 13 aspect ratio that makes it asbestiform 14 rather than just the fiber per se. 15 BY ATTORNEY IOLA: 16 Q Okay. Is it your opinion that if 17 something is a fibrous variety of one of these 18 asbestos mineral species but it is not 19 asbestiform, does it pose the same health risk 20 as a structure that's asbestiform? 21 A Well, I think, you know, we're 22 getting back to a couple of different questions 23 you asked earlier; right? If we talk about 24 fiber length, for example. You know, and if 25 it's a .1 micron length fiber, I don't think	Page 73 1 ratio -- that can be fibrous but not 2 asbestiform. 3 You seen that before; right? 4 A Yes. 5 Q Okay. From your perspective, if you 6 have a structure that meets those criteria and 7 it's one of the six regulated asbestos 8 varieties, it's 8 microns long by 0.25 microns 9 wide, 40-to-1 aspect ratio, is that a mineral 10 particle of health concern, from your 11 perspective? 12 A Well, I don't know. I mean, I think 13 I'd need more context, particularly because 14 you're asking questions about, you know, what 15 could be crushed fragments or something that 16 ended up, you know, in that particular size and 17 shape. And so I understand that there's -- you 18 know, that's still an evolving science, whether 19 that would be true. 20 So I think, you know, if it formed 21 that way -- and again, I don't want to get into 22 trying to pretend I'm a mineralogist -- but I 23 think it matters whether it was formed that way 24 in nature or whether it became that way through 25 some industrial process.

Page 74 1 Q Okay. And as you mentioned 2 earlier -- I guess the bow on top of this is the 3 jury's still out. The medical and scientific 4 literature is still unresolved as to whether or 5 not structures that are classified as 6 non-asbestiform but are fibrous pose the same 7 health risk as those that are classically 8 asbestiform? 9 ATTORNEY COWAN: Form. 10 BY ATTORNEY IOLA: 11 Q Is that right? 12 A I think there's not sufficient 13 evidence, from what I've seen, to answer the 14 question. 15 Q Okay. And I realize that there's a 16 lot more to this report than just this section. 17 But on page 32, the next section, entitled Talc, 18 do you, as a medical doctor, care about what 19 differences, if any, there are between the 20 so-called cosmetic talc and so-called industrial 21 talc? Does that matter to you? 22 A I mean it can. It can matter. 23 Q How? 24 A Well, if it's, if it's industrial 25 talc, for example, it, you know, it wouldn't be	Page 76 1 really the main place I'm talking about. 2 Q Okay. And for the -- for Gouverneur, 3 or the New York talc miner and miller studies, 4 however you want to classify them, have you seen 5 the Honda paper, the Hull paper? Those are both 6 from 2002. 7 A Yes, I have. 8 Q And you certainly saw the discussion 9 about that in the NIOSH roadmap in 2011; 10 correct? 11 A If it's in there, I'm sure I did. 12 But I don't recall that. 13 Q It's okay. Based on the New York 14 talc miner and miller epidemiology, do you agree 15 that it shows that talc contaminated with a 16 sufficient amount of asbestos and people exposed 17 for a sufficient duration to that product can 18 develop mesothelioma from it? 19 A So I'm not sure. I'd have to go back 20 to those because I know there's, like, a couple 21 of, like, letter-to-the-editor kind of things 22 from Finkelstein, like case report things. I 23 got to look again at Honda to recall all the 24 details. 25 I mean, to me, I think it suggested
Page 75 1 the type of talc that we would use in 2 pleurodesis; right? It's meant to be cosmetic 3 grade talc that's also been sterilized. So, you 4 know, as a source of talc, I don't think it 5 would make sense to, you know, reach out to, you 6 know, a commercial type of talc products. 7 And, you know, my general 8 understanding is that there's a different 9 percentage of non-talc that's allowable in 10 different, you know, definitions of that. 11 Q Uh-huh. 12 A And I think -- you know, I haven't 13 made a thorough study. But I've seen some 14 studies with so-called industrial talc where 15 there may well be, you know, asbestos and 16 asbestos of the form that we're talking about. 17 Q Okay. When you mention some studies 18 related to industrial talc where it may actually 19 contain asbestos, perhaps by any definition of 20 the word -- and which studies? In what context 21 have you seen that? 22 A Well, the Gouverneur talc, for 23 example, where I've seen, you know, evidence 24 that it, it may have, like, tremolite -- you 25 know, tremolite as part of that. So that's	Page 77 1 it was possible. But I don't know if I reached 2 a conclusion from when I looked at those 3 articles. 4 Q Okay. And I -- have you ever been 5 retained by RT Vanderbilt or Vanderbilt 6 Holdings, LLC in a case? 7 A I have not. 8 Q Okay. I guess I'll do this as a 9 hypothetical since I know you haven't seen this. 10 But I have had the experience of being in 11 multiple Vanderbilt trials. And I'll represent 12 to you that the uncontested testimony is that 13 there's at least 14 mesotheliomas in a cohort of 14 approximately 790 New York talc miners and 15 millers, which is approximately 1-and-a-half 16 percent of the total workforce. 17 Making that assumption, do you agree 18 with me that that is an epidemic of 19 mesothelioma? 20 A No. I mean it's, it's too simple; 21 right. In order to calculate what the risk is, 22 you need some comparison group. And they would 23 have to be -- if you say that it's a risk, you'd 24 have to compare them to some group that you 25 articulate and compared it to what the expected

Page 78 1 amount would be in the group. 2 So just with those simple facts, I 3 don't think it's -- I don't think it makes sense 4 just to make an assumption about that. 5 Q What is the background rate, if any, 6 of mesotheliomas in the general population, 7 people not exposed to anything other than -- 8 actually, let me ask it a different way. 9 What is the background rate of 10 mesotheliomas in the United States? You can 11 either do it per hundred thousand, per million, 12 whatever you're comfortable with. 13 A Yeah. I mean, currently -- it always 14 depends on sort of, you know, time and place and 15 so forth. But currently, I think there's about 16 3,000 mesotheliomas diagnosed each year and 17 there's about 300 million people, you know, in 18 the United States. So at least in terms of, you 19 know, an annual incidence, I think it would be 20 about one per hundred thousand people living in 21 the US. 22 Q Okay. So if you have a group of 800 23 workers, like in the New York talc miners and 24 millers, any reasonable control group you would 25 expect to see zero mesotheliomas in; right?	Page 80 1 epidemiology study of young children. 2 Q I think all I've seen are the case 3 reports too. I don't know if an epi study's 4 ever been done. But is it your opinion that the 5 occurrence of mesotheliomas in very young people 6 is more evidence to suggest that mesotheliomas 7 can occur spontaneously, absent any 8 environmental exposure? 9 A Yes. 10 Q Okay. Have you seen studies that 11 indicate in stillborn babies where fiber 12 digestions were done, asbestos fibers were found 13 in the stillborn babies, suggesting to the 14 authors that the mothers were exposed to the 15 asbestos and the fibers were actually traversing 16 the placenta in utero. Have you seen that? 17 A I think I have seen one that said 18 that. 19 Q Okay. There have also been some -- I 20 believe they were -- Bruce would know; he'll 21 correct me if I'm wrong -- but I believe that 22 they were either hamster or rat model studies 23 that confirm that asbestos fibers can traverse 24 the placenta in utero. Have you seen that? 25 A I don't recall seeing that.
Page 79 1 A No. I mean, the control group could 2 be the entire US population, in which case it 3 would be 3,000. 4 Q Oh, okay. I see your point. Okay. 5 You got me a little distracted thinking about 6 New York talc. Let me keep going. 7 A I didn't bring it up, by the way. 8 Q No, no. I did. I can't, I can't 9 help myself. Tom Radcliffe, who I don't know if 10 you know, he would hate me for that. 11 On page 44 and 45 you have 12 discussions about mesotheliomas in young 13 persons. And I can wait till you're there. 14 Just let me know when you're there. 15 A Yes. 16 Q Okay. There have been instances -- 17 well, let me ask it this way: Have you seen the 18 literature -- I think it's primarily out of 19 researchers from UT Austin -- studying 20 mesothelioma in very young children, like under 21 ten years old? 22 A I don't know that I've seen a study. 23 I've -- and I don't know where from. But I've 24 seen case reports of, you know, very young 25 children. But I haven't seen like an	Page 81 1 Q Okay. What evidence, if any, do you 2 have that mesotheliomas were occurring and being 3 diagnosed before the industrial use of asbestos 4 in the 20th century? 5 A Yeah, I don't have evidence of that. 6 But I haven't looked either. 7 Q Okay. There are two articles, one by 8 Dr. Strauchen about Mount Sinai Hospital and one 9 by Dr. Mark about Mass General, where they went 10 back and looked at autopsies before the 11 industrial use of asbestos and found no 12 mesotheliomas. Have you seen those papers? 13 A I have. 14 Q Okay. In the next section -- this is 15 the reason -- what prompted this discussion was 16 your discussion of the 2010/2012 IARC monographs 17 on talc. 18 Do you have an opinion one way or 19 another about whether or not particles where 20 talc is intergrown with anthophyllite -- 21 sometimes these are called transitional; 22 sometimes these are called biopyribole; 23 sometimes they're called intermediate fibers. A 24 lot of words to describe this, but they're 25 particles that have a mixture of talc plus an

Page 82 1 amphibole. 2 Do you have an opinion as to whether 3 those can be a cause of mesothelioma? 4 A I haven't seen evidence that they 5 can. I mean, I haven't seen epidemiology on 6 that topic. 7 Q Okay. And when IARC says talc 8 containing asbestiform fibers is a carcinogen, 9 do you have an opinion as to whether or not 10 asbestiform talc fibers are included in that 11 assessment? 12 A So I -- my opinion is that was a 13 clumsy statement. And I don't think that they 14 articulated it clearly enough. So what I've 15 seen is that, you know, in my view, that 16 plaintiff's attorneys like to use that statement 17 to imply that they did say definitively that 18 asbestiform talc is a carcinogen. 19 But, you know, it runs counter to 20 them also having a talc monograph that says that 21 talc's not a carcinogen. So, you know, to me, 22 talc is talc, right, so whether it's platy or 23 whether it's asbestiform. So those are 24 inconsistent with each other. 25 And there's one -- if you go -- I	Page 84 1 A That's correct. 2 Q And again, correct me if I'm wrong, 3 but one of the reasons why talc is a good agent 4 for a pleurodesis procedure is that it's 5 inflammatory; it irritates the pleural space, 6 causing the parietal and visceral pleura to 7 actually adhere so fluid can't build up. Right? 8 A Yeah; it causes acute inflammation. 9 Q And while we do not know the exact 10 mechanistic effects by which asbestos fibers 11 cause tumors, cause genetic damage leading to 12 tumors, one of the hypothesized pathways is due 13 to inflammation; right? 14 A Yeah. But chronic inflammation; 15 right? And so your lead-in to this was what's 16 the effect of talc in pleurodesis, which is 17 acute inflammation, right, a temporary effect 18 that achieves the desired result. And the 19 theory that you're talking about is chronic 20 inflammation. You know, it's ongoing. 21 Q Do you agree that fibrous talc itself 22 can cause pleural plaques? 23 A I don't, I don't believe that. 24 Q Okay. Are you familiar with the 25 disease talcosis?
Page 83 1 don't have the citation in front of me. But if 2 you look to the IARC website, there's a place 3 where you can go and they kind of list out, you 4 know, what some of their findings have been in 5 just summary form. And they talk about -- when 6 they link it to talc and then it says, you know, 7 with asbestiform -- or, I mean -- with 8 asbestiform fibers. And then they say in 9 parentheses: See asbestos. 10 So they link it conceptually to their 11 asbestos monograph. So as best as I can tell, I 12 think you're talking about asbestos, per se, in, 13 in talc. But I agree that their statement's 14 ambiguous and that it's, you know, up for 15 interpretation. 16 Q Okay. And perhaps we'll get some 17 clarity on that, because I think they just 18 met -- the talc group just met, I think two 19 weeks ago. So maybe we'll get an update to that 20 in the next couple months. 21 But let me ask about fibrous talc for 22 a minute, actually, while we're on the subject. 23 You mentioned that, I think in your clinical 24 practice, in your everyday job, you've used talc 25 for pleurodesis procedures; correct?	Page 85 1 A Yes. 2 Q And that is an interstitial scarring 3 of the lung by talc itself; correct? 4 A That's correct. 5 Q It's the -- it occurs in roughly the 6 same areas that someone might get asbestosis 7 from asbestos exposure; correct? 8 A Well, it's the lung and it's the 9 interstitium, which is every part of the lung, 10 per se, but the airways. 11 Q And I really should know this, but 12 are you a B reader, sir? 13 A There's no need to be one, and I'm 14 not one. 15 Q Okay. No judgment. I'm just asking. 16 I know most people aren't, but -- 17 A You can judge. But I'm just saying 18 I'm not and there's no value to it for me in 19 clinical practice. 20 Q I understand. And I am not. 21 But you do look at the imaging; 22 right? You looked at the imaging in this case 23 that was available to you; correct? 24 A Absolutely. 25 Q You're familiar with what asbestosis

Page 86 1 looks like on imaging versus what talcosis looks 2 like; right? 3 A Yes. 4 Q And they can look pretty similar, 5 can't they? 6 A Sure; the pattern can be the same. 7 Q Okay. All right. Are you familiar 8 with -- in the early 1990s, the FDA, in 9 combination with the National Toxicology 10 Program, had a two-day talc conference. I 11 believe it was 1993 or 1994. One day was about 12 ovarian cancer. One day was basically about 13 other health effects and asbestos. 14 Have you seen that? Have you seen 15 those from those conferences? 16 A I'm going to say maybe. I mean, I've 17 seen a lot of stuff. I'm not sure if I've seen 18 that. 19 Q Okay. Are you aware that as part of 20 that, the NTP did a chronic inhalation animal 21 model and found an increased risk of pulmonary 22 carcinomas? 23 A Well, they found adenomas, I think. 24 And they also found pheochromocytomas, which is 25 not lung cancer. But, you know, I'm familiar	Page 88 1 cannot rule out a contribution to meso from any 2 asbestos exposures he might have had from his 3 work history; correct? 4 A That's correct. 5 Q I know you've done this a bunch. You 6 probably know what I'm going to can ask. But 7 can you go any further than just you can't rule 8 it out and it's possible? 9 A I cannot. 10 Q Okay. And I think you and I have 11 kind of -- correct me if I'm wrong -- you and I 12 have kind of narrowed the scope of what we're 13 really talking about in terms of the work 14 history. We're really -- your primary concern 15 in terms of the work history that you are not 16 ruling out but also not taking any further than 17 that is any occupational exposures he might have 18 had associated with the hotel work, basically in 19 the 1980s; right? 20 A That's correct. And I think there's 21 a couple of years, perhaps in the early 2000s, 22 the other part of that work experience, that 23 could have still contributed. 24 Q Okay. Are you able to tell me with 25 specificity the name brand, manufacturers, or
Page 87 1 with that study and, you know, some of the 2 commentary that's followed that study. 3 Q Okay. All right. I think we're 4 getting towards the end, and I'll wrap up here 5 very quickly. 6 Towards the end you have -- starting 7 on page 62 is, as I understand it, your 8 assessment of Mr. Perry's mesothelioma and the 9 potential causes of it; correct? 10 A That's correct. 11 Q Your conclusions as to Mr. Perry are 12 as follows -- at least in part; I know there are 13 others that I'm not listing here -- first, that 14 there is no objective evidence that Mr. Perry 15 had exposure to asbestos from any of the talc 16 products; right? 17 A That's correct. 18 Q And assuming -- even assuming that 19 Mr. Perry did have some levels of asbestos 20 exposure to some talc products that he used over 21 time, that would not have been enough to 22 increase his risk of mesothelioma, even pleural 23 mesothelioma; correct? 24 A That's correct. 25 Q It's also your opinion that you	Page 89 1 even types of asbestos-containing products that 2 he would have had the potential to be exposed to 3 while at work? 4 A Well, certainly not any name brands. 5 I mean, the potential, I think you mentioned, 6 like, drywall and I think maybe tape and some 7 other things related to some of the other 8 renovations. 9 Q Uh-huh. 10 A And then the potential -- you know, 11 if there is -- whatever's in the library, the 12 potential was all kinds of things; right? It 13 could be -- you know, could be insulation on 14 pipes and so forth. But I don't have any 15 information specifically what those exposures 16 would have been. 17 Q Okay. And the library timeframe is 18 approximately like 2000 and 2001; is that right? 19 A That's right. 20 Q So it's kind of right on the edge of 21 what you told us is the requisite amount of time 22 necessary away from the diagnosis to contribute; 23 right? It's like right on that 20-year edge? 24 ATTORNEY COWAN: Form. 25 THE WITNESS: That's correct.

Page 90 1 BY ATTORNEY IOLA: 2 Q Okay. You're not able to tell me 3 what asbestos fiber types were present at any of 4 the locations where Mr. Perry might have had 5 occupational exposures to asbestos? 6 A Not as a fact, no. 7 Q Okay. And you would agree with me 8 that by the 1980s, the vast majority of products 9 that had traditionally contained asbestos 10 earlier in time had been -- the asbestos had 11 been replaced with another substitute -- for new 12 products; right? 13 A Yeah. With the qualification for new 14 products, that's right. 15 Q So the opportunity for exposure to 16 commercial amphibole asbestos in the 1980s by 17 Mr. Perry is basically limited to products that 18 might be in place from an earlier timeframe, 19 probably 10 or 15 years earlier than he was 20 there; right? 21 A Yeah. So sort of, like, legacy 22 products that might have been on-site. 23 Q Okay. And any amphibole asbestos 24 that Mr. Perry might have been exposed to in the 25 early 2000s suffers from the same problem, which	Page 92 1 written that show a no observed effect, you 2 know, of asbestos and mesothelioma, for example, 3 and lung cancer. 4 Q Okay. And you find both the original 5 NOAEL paper and the updated paper by Pierce and 6 co-authors, you find those papers to be 7 authoritative and reliable? 8 A So I don't use the word 9 "authoritative" because I understand it has a, 10 like a legal connotation. So in my fields, I 11 don't find anything to be authoritative. Even 12 guidelines -- you know, guidelines are 13 guidelines; right? They're hopefully well 14 thought out suggestions. But, you know, other 15 than maybe -- well, "authoritative" I think 16 belongs in the legal world. 17 Q Okay. 18 A But I do find those papers to be 19 credible. I mean they're -- they -- you know, 20 to a fault, they're incredibly wordy in terms of 21 what their methodology was. But I think 22 they've -- you know, they've articulated what 23 they did, I think, and, you know, the reader can 24 follow and see what they did. A reader can, you 25 know, pull the same papers that they've cited
Page 91 1 is it wouldn't be new products going in. It 2 would have been legacy products, and at that 3 point it would have had to have been present for 4 decades; right? 5 A That's correct. 6 Q Do you -- there are certain 7 experts -- and I'm sure you've seen this in 8 Dr. Pierce's reports and Dr. Sahmel's reports 9 and Dr. Nony's reports that they subscribe to 10 what's referred to as the "no observable adverse 11 effects levels" for cumulative exposures to 12 asbestos for each fiber type. You've seen that; 13 right? 14 A I have. 15 Q Do you agree with their 16 assessments that -- well, let me stop there. 17 Do you agree with their assessment 18 that there are no observable adverse effect 19 levels for different asbestos fiber types? 20 A Well, yeah. I mean, I've read the 21 Pierce papers and the more recent Beckett one 22 and I've read, you know, all of the articles 23 that they cite, you know, as part of their 24 analysis. And there clearly are papers that 25 underpin, you know, those papers that they've	Page 93 1 and then can, you know, decide if they agree 2 with their conclusions or not. 3 And they also have, you know, a 4 really extensive, you know, recitation of the 5 strengths and limitations of their findings and, 6 you know, what might be an overestimate, what 7 might be an underestimate. 8 So, yeah, I think that they've done a 9 very thorough and credible job of articulating 10 what they've done. 11 Q Okay. Any exposures that Mr. Perry 12 might have had in his lifetime -- and we can 13 treat them cumulatively -- the cumulative effect 14 of any exposures that Mr. Perry would have had 15 in his lifetime to chrysotile asbestos did not 16 increase his risk of mesothelioma or contribute 17 to his risk of mesothelioma; correct? 18 A So I think -- you know, I know that 19 there's people that talk that way. I don't 20 think cumulative exposure causes anything; 21 right? I think cumulative exposure is an 22 estimate of what somebody's dose may have been 23 to something. But it's not the fact, you know, 24 of what caused somebody's disease. 25 But I think what -- if I can sort of

Page 94 1 maybe reframe it, you know, I don't see evidence 2 that there was a dose of chrysotile asbestos 3 that contributed to his risk of developing 4 mesothelioma, you know, based on the materials 5 in the case. 6 Q Okay. Do you agree that a reasonable 7 layman explanation of what cancer is, is a 8 loss -- it's uncontrolled cell growth, a loss of 9 orderly cell division? 10 A Yeah, I think that's part of it. And 11 it's a helpful way to describe. 12 Q And for mesothelioma, you have to 13 have multiple genetic errors before you get 14 tumor formation. Is not like you can just get 15 one. You have to have three, four, five -- I 16 know people may disagree about the specific 17 number. 18 A Yeah, I don't know -- I mean, we're 19 talking about driver mutations. And I don't 20 know if it's known for sure what the number is, 21 you know, but likely more than one. 22 Q Okay. Is it possible for someone to 23 have exposure to asbestos and a germline 24 mutation that's an independent cause of 25 mesothelioma where the asbestos contributes to	Page 96 1 those two expert reports. 2 Q Okay. I ask this next question with 3 the caveat that obviously you cannot predict 4 what myself or another plaintiff lawyer might 5 ask you at trial or even necessarily what a 6 defense lawyer might ask you at trial. 7 But setting that aside for a second, 8 have you attempted to put all of the opinions 9 and the bases of your opinions that you intend 10 to testify at trial into these two reports, 11 along with all the -- you know, the cited 12 materials incorporated therein? 13 A Yeah. I have -- I'd say the main or 14 overarching primary, you know, opinions I've 15 tried to articulate and tried to provide 16 sufficient information to support those. 17 ATTORNEY IOLA: Okay. Doctor, those 18 are all the questions I have. Thank you 19 for your time this morning. 20 THE WITNESS: Of course. Thank you. 21 ATTORNEY IOLA: Chris? Anybody else? 22 ATTORNEY COWAN: We'll be reserving 23 for trial. Thank you. 24 BY ATTORNEY RAINSFORD: 25 Q Doctor, I do have a quick couple of
Page 95 1 one genetic error, the germline mutation 2 contributes to another, and they work 3 cooperatively to cause the tumor ultimately? 4 A So that's not what the word 5 "cooperatively" means. I mean, I think -- you 6 know, you can have a germline mutation that -- 7 because of what you're born with genetically, 8 and you can induce one, you know, from a 9 sufficient asbestos exposure. 10 If "cooperative" means that there's 11 an interaction or some kind of synergy, I'm not 12 sure that that's true. But up until that point, 13 I agree that each of those, you know, each of 14 those could contribute a driver mutation. 15 Q Okay. Okay. Let's see. I'm just 16 looking briefly at your July 2nd, 2024 report, 17 Doctor. As I understand it, this report was to 18 summarize additional materials that had been 19 provided to you after issuance of your first 20 report. Is that accurate? 21 A That's exactly right. 22 Q Okay. And what I saw is it was 23 primarily a couple of additional expert reports; 24 is that accurate? 25 A I think it was only -- yeah, only	Page 97 1 questions. It's just kind of a housekeeping 2 matter, if you've got a moment. 3 My name is Todd Rainsford. I 4 represent PTI Royston in this case. And there's 5 some apparent confusion in your reports and your 6 testimony earlier today regarding PTI Royston 7 versus PTI Union as a blender of Ammens and Gold 8 Bond products. 9 I'll represent to you that 10 PTI Royston never blended Ammens and Gold Bond 11 products but PTI Union did. With that in mind, 12 could you have been confusing PTI Royston and 13 PTI Union in your initial June 27th report and 14 in your testimony this morning? 15 A Oh, sure. Yeah. I mean, I'm not a, 16 I'm not a scholar of, you know, different 17 corporate entities and their names and so forth. 18 So, yeah, I definitely could have used the 19 wrong, the wrong version of PTI in my report and 20 in my testimony. 21 Q Okay. So with that in mind, would it 22 be accurate, then, to say that any references 23 made to PTI Royston, either in your June report 24 or in your testimony today, should have been to 25 PTI Union instead?

Page 98		Page 100	
1	A Yeah. I mean, assuming that what	1	ERRATA
2	you're telling me is right, you know, that --	2	PAGE LINE NOTATION
3	ATTORNEY RAINSFORD: Okay. Thanks.	3	_____ - _____ - _____
4	That's all I've got.	4	_____ - _____ - _____
5	ATTORNEY IOLA: Anybody else?	5	_____ - _____ - _____
6	DEFENSE COUNSEL: No questions.	6	_____ - _____ - _____
7	ATTORNEY IOLA: All right. Hearing	7	_____ - _____ - _____
8	none, I think we can go off the record,	8	_____ - _____ - _____
9	Adam.	9	_____ - _____ - _____
10	Doctor, thank you for your time this	10	_____ - _____ - _____
11	morning.	11	_____ - _____ - _____
12	ATTORNEY PECK: Sam, this is Tim	12	_____ - _____ - _____
13	Peck. Sorry; I couldn't get to my button	13	_____ - _____ - _____
14	quick enough. I just have that brief	14	_____ - _____ - _____
15	statement to put on the record as well, if	15	_____ - _____ - _____
16	all the questions are finished.	16	_____ - _____ - _____
17	ATTORNEY IOLA: Fire away, Tim.	17	_____ - _____ - _____
18	ATTORNEY PECK: And this is really	18	_____ - _____ - _____
19	just for the record, for Adam.	19	_____ - _____ - _____
20	I represent the defendant American	20	_____ - _____ - _____
21	International Industries, and it's	21	_____ - _____ - _____
22	frequently referred to as AII. AII would	22	_____ - _____ - _____
23	have had questions for Dr. Diette today	23	_____ - _____ - _____
24	but for the Court's May 29th, 2024 order	24	_____ - _____ - _____
25	that placed limitations upon AII's	25	_____ - _____ - _____
Page 99		Page 101	
1	preparation of its defense, including its	1	C E R T I F I C A T I O N
2	examination of expert witnesses and its	2	
3	ability to conduct discovery generally.	3	
4	That said, AIA reserves its right to	4	I hereby certify that I have read the
5	fully examine Dr. Diette at a later time	5	foregoing transcript of my deposition
6	if the Court's ruling should be changed.	6	testimony, and that my answers to the
7	Thank you.	7	questions propounded, with the attached
8	ATTORNEY IOLA: All right. Thanks,	8	corrections or changes, if any, are true and
9	Tim. I think we're done.	9	correct.
10	(Deposition concluded at 11:55 a.m.)	10	
11		11	-----
12		12	GREGORY B. DIETTE, MD, MHS
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C E R T I F I C A T I O N

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I, ADAM D. MILLER, Registered
Professional Reporter, certify that the
foregoing is a true and accurate transcript
of the foregoing deposition, that the
witness was first sworn by me at the time,
place and on the date herein before set
forth.

I further certify that I am neither
attorney nor counsel for, not related to nor
employed by any of the parties to the action
in which this deposition was taken; further,
that I am not a relative or employee of any
attorney or counsel employed in this case,
nor am I financially interested in this
action.



/s/ Adam D. Miller
Registered Professional Reporter
and Notary Public