UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION	**Civil Action No. 3:16-md-2738-FLW-LHG** **MDL No. 2738**

THIS DOCUMENT RELATES TO ALL CASES

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I. INTRODUCTION AND BACKGROUND

The Plaintiffs' Steering Committee ("PSC") respectfully submits this Memorandum in further support of the admissibility of its experts' opinions and inadmissibility of certain of the expert opinions offered by Defendants Johnson & Johnson and Johnson & Johnson Consumer Inc. (collectively "J&J") on the issue of whether Defendants' Baby Powder and Shower-to-Shower products ("talcum powder products" or "TPP") can cause ovarian cancer.[1] This MDL involves thousands of women who allege their use of TPP caused ovarian cancer. The only question presently before the Court is whether the expert opinions are admissible under Fed. R. Evid. 702 and *Daubert*.[2]

Fed. R. Evid. 702 and *Daubert* do ***not*** concern which expert is correct.[3] That is a question for the trier of fact. Instead, the Court need only determine whether the opinions are proffered by sufficiently qualified experts, who apply reliable

[1] *See, e.g.*, ECF No. 9732 ("PSC's Omnibus Brief") and ECF No. 9914 ("PSC's General Causation Opposition Brief") (correcting version ECF No. 9888). Although only certain of the PSC's experts testified at the *Daubert* Hearing, the PSC maintains the admissibility of all its proffered experts. The PSC also stands by its motions to exclude certain opinions of J&J's expert witnesses. The PSC relies upon and incorporates by reference its prior briefing on these issues.

[2] *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993).

[3] *See, e.g., In re Paoli R.R. Yard PCB Litig. ("Paoli II")*, 35 F.3d 717, 744 (3d Cir. 1994) (noting a party does "not have to demonstrate to the judge by a preponderance of the evidence that the assessments of their experts are correct, they only have to demonstrate by a preponderance of evidence that their opinions are reliable").

methodology in reaching their conclusions, and whose testimony will assist the trier of fact.[4] The PSC's experts readily meet this standard.

The PSC's experts are highly qualified in their respective fields and arrived at their opinions by applying well-accepted methodologies, including analysis of the totality of the scientific and medical literature, application of the Hill Guidelines,[5] and application of current understandings of etiology, study design, and statistical analysis. The PSC's experts methodically and painstakingly worked from the ground-up and:

- analyzed all relevant peer-reviewed epidemiology;
- examined the constituents in TPP and their effects on the human body;
- evaluated the relevant peer-reviewed literature concerning biologically plausible mechanisms, including evidence of how TPP gets to the ovaries and fallopian tubes;
- evaluated the biological effects of exposure to TPP on ovarian and fallopian cells; and,
- evaluated the scientific data related to inflammation and carcinogenicity in the context of ovarian cancer.

In its briefing, J&J attacks the PSC's experts on all fronts, arguing that every aspect of the PSC's experts' opinions is the product of unreliable methodology.

[4] *See, e.g., JVI, Inc. v. Truckform Inc.*, No. CIV. 11-6218 FLW, 2012 WL 6708169, at *4 (D.N.J. Dec. 26, 2012) (*citing Calhoun v. Yamaha Motor Corp., U.S.A.*, 350 F.3d 316, 321 (3d Cir. 2003)).

[5] Hill, *The Environment and Disease: Association or Causation?* 58 Proc. Royal Soc'y Med. 295 (1965) ("Hill Guidelines"), ECF No. 9914, Ex. 1.

However, the testimony presented during the *Daubert* Hearing revealed that the parties' experts substantially agree on appropriate methodologies for determining causation. Therefore, J&J's expert challenges amount to nothing more than disagreements about the conclusion drawn from the body of scientific evidence, which go to the weight of the PSC's experts' opinions, not their admissibility. To the extent J&J's experts' opinions remain based on unreliable methodologies, the PSC stands by its motions to exclude those opinions.

II. THE PSC'S EXPERTS' GENERAL CAUSATION OPINIONS ARE ADMISSIBLE

A. THE PSC'S EXPERTS EMPLOYED RELIABLE METHODOLOGIES IN ASSESSING OBSERVATIONAL AND BIOLOGIC EVIDENCE

The PSC's experts considered and assessed the observational and biological data using reliable processes and methods. Those that testified at the *Daubert* Hearing provided additional support and foundation for their opinions and the opinions of the PSC's other experts.

1. Anne McTiernan, MD, PhD

Anne McTiernan is a medical doctor and renowned epidemiologist, specializing in women's health and cancer epidemiology.[6] Over her almost forty-year career, she has never served as a litigation expert.[7] After completing her analysis

[6] McTiernan Hr'g Tr. at 714:12-15; *see also* Expert Report of Anne McTiernan, MD, Ph.D. at 3, ECF No. 9914, Ex. 2.
[7] McTiernan Hr'g Tr. at 720:14-721:2.

and because of her expertise, Dr. McTiernan was asked by regulatory and scientific authorities, including the U.S. Congress and Health Canada, to provide her opinions about whether TPP can cause ovarian cancer.[8] This included publicly testifying before Congress regarding her assessment of the epidemiology and biologically plausible mechanisms for how TPP can cause ovarian cancer.[9]

Dr. McTiernan described her methodology for conducting her systematic review and analysis.[10] She collected and considered all of the epidemiologic studies relevant to talc and ovarian cancer, regardless of design, and analyzed each study's strengths and weaknesses. She found recall bias an unlikely explanation for the case-control study results because the risk is correlated with a specific histologic cancer subtype and there is "consistency across studies."[11] Like the International Agency for Research on Cancer (IARC), she similarly found chance and confounding unlikely.[12] She also considered the risk of non-differential misclassification biases in the cohort studies and testified that the risk of attenuation was significant,[13] an opinion that is consistent with the Taher authors and Health Canada.[14]

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[8] *Id.* at 721:3-726:3; McTiernan Hr'g Slides at 5-8, attached as **Post-Daubert ("PD") Exhibit 1**.
[9] McTiernan Hr'g Tr. at 723:19-725:24.
[10] *Id.* at 726:4-731:20; McTiernan Hr'g Slides at 9.
[11] *Id.* at 775:11-776:2.
[12] *Id.* at 758:5-760:3.
[13] *Id.* at 949:13-950:12.
[14] *See* Taher et. al, *Critical review of the association between perineal use of talc powder and risk of ovarian cancer*, 90 Reproductive Toxicology 88, 97 (2019),

Dr. McTiernan also addressed each of the nine Hill Guidelines.[15] For ***strength***, she opined that the results across studies showed a 22-31% increased risk, a magnitude similar to other known carcinogens.[16] For ***consistency***, her forest plots showed consistency of relative risk of observational studies, both for ovarian cancer, generally, and serous ovarian cancer, specifically.[17] On ***dose-response***, she opined that there was evidence of it, including from the Terry, Penninkilampi, and Berge studies.[18] With respect to ***biologic plausibility***, she showed that a causal explanation for the association was evidenced in the epidemiologic studies since: (1) TPP contains known carcinogens, including asbestos, fibrous talc, and heavy metals; (2) talc and other particles reach the ovaries through migration and inhalation; and, (3) TPP can cause oxidative stress and inflammation, both of which are known to be involved with carcinogenesis.[19] She also testified that the other factors were met, though they were of less importance.[20] Having reviewed the totality of the evidence,

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attached as **PD Exhibit 2**; Health Canada, Draft Screening Assessment, Talc 28 (December 2018), ECF No. 9914, Ex. 62.

[15] *See* McTiernan Rep. at 25-30, 63-68; *see also* McTiernan Hr'g Slides at 29 ("Bradford Hill Guidelines: Findings and Weight"); McTiernan Hr'g Tr. at 777:9-778:7 ("I did consider them all.").

[16] *Id.* at 778:8-780:12.

[17] *Id.* at 780:13-781:17; *see supra* n. 82.

[18] McTiernan Hr'g Tr. at 791:2-798:13.

[19] *Id.* at 781:8-790:17.

[20] *Id.* at 799:2-800:6.

Dr. McTiernan concluded, to a reasonable degree of scientific certainty, that TPP can cause ovarian cancer.[21]

2. Daniel Clarke-Pearson, MD

Dr. Clarke-Pearson is certified by the American Board of Obstetrics and Gynecology as a specialist in gynecology as well as a subspecialist in gynecologic oncology. He has dedicated his entire career to academic medicine, including chairing the University of North Carolina's Department of Obstetrics and Gynecology.[22] While his hearing testimony specifically focused on aspects of biologic plausibility, Dr. Clarke-Pearson performed a full Hill causation analysis, considering both the epidemiologic evidence and the biologic evidence.[23] He started by looking at the epidemiologic literature, "which is fairly extensive, and goes through several decades" and, after looking at the epidemiology, reviewed the biologic literature as to "what the mechanism might be that talcum powder can cause ovarian cancer."[24] As he stated, the methodology is similar to "what I do with an evidence–based medicine decision analysis…"[25]

[21] *Id.* at 719:5-720:13.
[22] Clarke-Pearson Hr'g Tr. at 1519:19-1525:6.
[23] *See generally* Clarke-Pearson Rep. at 1-10, ECF No. 9914, Ex. 12; Clarke-Pearson Hr'g Slides at 5, 8-9, attached as **PD Exhibit 3**.
[24] Clarke-Pearson Hr'g Tr. at 1531:10-1532:14.
[25] *Id.* at 1532:8-1532:14.

With respect to his review of the epidemiology, Dr. Clarke-Pearson reliably analyzed decades of case-control and cohort studies on TPP and ovarian cancer but placed greater weight on the meta-analyses, particularly the most recent published meta-analyses like Berge (2018) and Penninkilampi (2018).[26] Applying the Hill Guidelines, he found the strength and consistency of association "critically important" and specificity satisfied, as there was "overwhelming support in the epidemiologic literature that talcum powder statistically increased a woman's risk of developing epithelial ovarian cancer by about 30 percent."[27] Regarding temporality, Dr. Clarke-Pearson was clear that this aspect was supported by the evidence and consistent with the "clear latency period sometimes decades from the exposure to talcum powder in this case to the development of obvious ovarian cancers."[28] He further noted, with respect to dose-response, that some of the studies do not address the issue. However, for those that did, "both frequency and duration of use" demonstrate that "there is a dose response."[29] After addressing the epidemiologic evidence, Dr. Clarke-Pearson analyzed biologic plausibility and found it satisfied for three reasons:[30] ***first***, it is plausible that talcum powder can

[26] *Id.* at 1532:15-1542:2.
[27] *Id.* at 1542:2-20; Clarke-Pearson Hr'g Slides at 8-9.
[28] Clarke-Pearson Hr'g Tr. at 1542:21-1543:6.
[29] *Id.* at 1543:7-12.
[30] *Id.* at 1696:21-1697:17.

reach the ovaries and fallopian tubes through migration[31] or, less likely, through inhalation;[32] ***second***, it is plausible that once at the ovary and fallopian tube, TPP can induce oxidative stress and inflammation, both known to be associated with the development of ovarian cancer;[33] and ***third***, TPP contains known carcinogens like fibrous talc, asbestos, heavy metals, and other chemicals.[34]

J&J's cross-examination of Dr. Clarke-Pearson focused on issues affecting the weight to be accorded his causal analysis, not his qualifications or his methodology. For example, Dr. Clarke-Pearson was questioned on when he developed his talcum powder opinions[35] and about how and by whom he was contacted to be an expert in these MDL proceedings.[36] He was also questioned as to why he agreed with selected statements of certain authors and not others,[37] why he agreed with statements of certain regulators and not others,[38] and why organizations

[31] *Id.* at 1558:16-1563:15.
[32] *Id.* at 1663:16-1565:10, 1694:10-1695:19.
[33] *Id.* at 1545:8-1553:2, 1565:11-1570:20.
[34] *Id.* at 1570:20-1571:24.
[35] *Id.* at 1574:2-1586:9.
[36] *Id.* at 1592:23-1595:15.
[37] *Compare id.* at 1647:10-1648:20 (Berge authors did not believe that cause was supported), *with* 1538:11-1540:18, 1711:3-1712:9 (Penninkilampi concludes that the evidence supports causation).
[38] *Compare id.* at 1725:1-10 ("Health Canada reached a conclusion very similar to mine"), *with id.* at 1617:15-1619:19 (citing 2014 FDA denial of a Citizens petition).

like ACOG and NCI had not performed a complete causal analysis like he had.[39] Such challenges are not Rule 702 challenges, but are classic jury issues.

In the end, Dr. Clark-Pearson's evidence-based causation analysis resulted in his ultimate conclusion on causation: "genital application of talcum powder, such as Johnson & Johnson's Baby Powder and Shower-to-Shower, increases the risk of epithelial ovarian cancer in all women and can cause epithelial ovarian cancer in some women."[40]

3. Arch Carson, MD, PhD

Dr. Arch Carson, a medical doctor that specializes in medical toxicology, also performed a full risk assessment and causation analysis using the Hill Guidelines.[41] Despite his full causation analysis, and because of the nature of the *Daubert* hearing, his testimony focused on whether it "makes sense" or is biologically plausible to conclude that the association seen in the epidemiologic studies is causal in light of evidence that J&J's TPP contain asbestos, fibrous talc, heavy metals, and other carcinogenic chemicals.

[39] *Id*. at 1595:16-1603:25 (ACOG), 1608:16-1617:14, 1702:7-1705:23 (NCI).
[40] *Id.* at 1530:2-1530:6.
[41] *See* Carson Rep. at 1-11, ECF No. 9914, Ex. 18; Carson Hr'g Slides at 2, 22-23, attached as **PD Exhibit 4**; Carson Hr'g Tr. at 1258:19-1259:10, 1284:14-20 (qualifications), 1260:23-1262:14 (methodology), 1310:4-1314:23 (Hill analysis).

With respect to his opinion that "regular genital use of Johnson & Johnson's Baby Powder and Shower to Shower can cause epithelial ovarian cancer,"[42] the cross-examination of Dr. Carson focused on the weight to be accorded in light of what science does not, and cannot, show. For example, in order for an opinion to be reliable, it is not necessary to establish: the exact dose of TPP a particular woman has to use in order to place her at risk;[43] how to precisely measure exposure or the specific amount of TPP reaching the ovaries and fallopian tubes;[44] or, the similarity between the epidemiology of TPP studies and ovarian cancer and asbestos studies on the same issue.[45] Such challenges are not Rule 702 challenges, and more appropriately left for cross-examination at trial.

B. THE PSC'S EXPERTS APPLIED GENERALLY ACCEPTED PRINCIPLES AND METHODS FOR DETERMINING CAUSE AND EFFECT

1. The PSC's experts properly applied the Hill Guidelines

The parties agree that the Hill Guidelines provide a reliable methodology for assessing cause and effect. Broadly, the Hill Guidelines include: (1) strength of association; (2) consistency of association; (3) specificity of the association; (4)

[42] *Id.* at 1259:13-1260:22.
[43] *Id.* at 1317:8-1318:9.
[44] *Id.* at 1323-1334:24.
[45] *Id.* at 1348:21-1353:5.

temporality; (5) biologic gradient or dose-response; (6) biologic plausibility; (7) coherence with existing knowledge; (8) experiment; and (9) analogy.[46]

The parties' experts also agree that reliable consideration of the Hill Guidelines does not require their mechanical application and the absence of any one factor (except temporal relationship) does not prevent a finding of causation.[47] Instead, these nine factors are "***guidelines***" that must be "***coupled with reasoned judgment*** about the entire body of available evidence, in making decisions about causation."[48] Under the correct standard, "[e]qually competent scientists, examining the same information, can arrive at different conclusions" about causality.[49]

Yet, J&J and its experts argue for a heightened standard of proof by faulting the PSC's experts for their opinions that strength of association, consistency, dose-response, and biological plausibility were satisfied, based on disagreements of how

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[46] Hill (1965) at 295-299; *see also* McTiernan Hr'g Tr. at 729:12-16, 777:9-778:7; Clarke-Pearson Hr'g Tr. at 1542:2-1547:7; Diette Hr'g Tr. at 1071:16-21, 1076:15-1078:23.

[47] *See* Kenneth Rothman, et al., *Modern Epidemiology* at 2-32 (3d ed. 2009), ECF No. 9914, Ex. 20; Leon Gordis, *Epidemiology* at 243-261 (5th ed. 2013), ECF No. 9914, Ex. 133; McTiernan Hr'g Tr. at 777:25-778:14; Diette Hr'g Tr. at 1076:15-20 ("it is not a checklist with boxes").

[48] Gordis, *Epidemiology* at 260 (emphasis added); *see also* McTiernan Hr'g Tr. at 726:4-731:30, 777:7-778-7 ("reasoned judgment" should be applied to Hill Guidelines) *and* McTiernan Hr'g Slides at 9; Diette Hr'g Tr. at 1078:13-19, 1075:25-1076:14 ("agree[d] with it completely" that judgment is a critical part of the Hill Guidelines and that experts exercising judgment may disagree as to the strengths and weaknesses of epidemiologic studies).

[49] Jack Siemiatycki, Ph.D., *Risk factors For Cancer In the Workplace* at 298 (1991), ECF No. 9737-1, Ex. 74.

the underlying epidemiology should be interpreted. As is clear from their reports, deposition testimony, and hearing testimony, the PSC's experts properly considered the Hill Guidelines using their reasoned judgment of the evidence:

- **Strength:** There is no threshold risk ratio for strength of association.[50] At the *Daubert* Hearing, Dr. McTiernan testified that there is "no threshold," and described two examples – hormone replacement therapy ("HRT") and second-hand smoke – which have risk ratios in the 20% and 60% range.[51] J&J's expert, Dr. Diette, agrees "[t]here isn't an exact cut-off" and acknowledges the low risk ratios for second-hand smoke and HRT.[52] Dr. Diette's attempt to distinguish the quality of evidence supporting the strength of association for second-hand smoke and HRT from TPP, goes to weight, not admissibility.[53]

- **Consistency:** Statistical significance across studies is not the metric of consistency.[54] In fact, it is recognized as a "mistake" to state that a "set of results is inconsistent simply because some results are 'statistically significant' and some are not."[55] As Dr. McTiernan explained, consistency is "driven by the relative risk" (RR) and the "tightness" of the confidence intervals (CI's).[56] While she considered statistical significance, Dr. McTiernan testified that it would be methodologically "inappropriate to dismiss" non-statistically significant RR's as part of a consistency assessment.[57] While Dr. Diette deflected the relevance of statistical

[50] ECF No. 9914 at 134-138; Rothman, et al., *Modern Epidemiology* at 26.
[51] McTiernan Hr'g Tr. at 778:8-780:12 (describing specific RR for HRT and general range for second-hand smoke); *see also* ECF No. 9914 at 140 (chart identifying causes of cancer with risk ratios between 9-72%).
[52] Diette Dep. at 362:6-15, 377:24-381:11 (acknowledging U.S. Surgeon General report of 1.2-1.3 RR for second-hand smoke), ECF No. 9737-1, Ex. 9; *see also* Diette Hr'g Tr. at 1027:22-25, 1029:4-12.
[53] Diette Hr'g Tr. at 1029:4-1031:12.
[54] ECF No. 9737-1 at 7-47; ECF No. 9914 at 91-131.
[55] Rothman, et al., *Modern Epidemiology* at 27; *see also* Wasserstein & Lazar, *The ASA's Statement on p-Values: Context, Process, and Purpose*, 70 Am. Statistician 129, 129-131 (2016), ECF No. 9914, Ex. 142, and Amrhein et al., *Retire Statistical Significance*, 567 Nature 305 (2019), ECF No. 9914, Ex. 138.
[56] McTiernan Hr'g Tr. at 746:3-754:13.
[57] *Id.* at 751:19-24, 933:14-935:24.

significance in the context of the Hill Guidelines to irrelevant issues,[58] he ultimately agreed that it is improper in assessing consistency to "line [studies] up and say these [studies] are [statistically significant] and these are not."[59]

- **Dose-Response:** Dose-response does not require a showing of a "consistent statistically significant increased risk",[60] as argued by at least some of J&J's experts (*i.e.*, Dr. Ballman).[61] Rather, any evidence of dose-response is useful. Dr. Diette agreed that the Hill Guidelines do not require a statistically significant increased risk for dose-response for this guideline to be met.[62]

- **Biologic Plausibility:** All experts agree biologic plausibility does not require proof.[63] While much of J&J's focus at the *Daubert* Hearing was on whether the PSC had proven the mechanism by which TPP actually causes ovarian cancer, all expert witnesses agreed that biologic plausibility looks at whether it "makes sense" that the association is causal based on what is known biologically about the product or disease.[64]

2. The PSC's Experts Reliably Applied Epidemiological Principles In Their Analyses

a. J&J's "Hierarchy of Evidence" Is An Improper Methodology

There are no randomized clinical trials studying TPP and ovarian cancer because such studies would be impractical and unethical.[65] Therefore, observational

[58] Diette Hr'g Tr. at 1146:13-1152:12 (FDA drug approval and journal publication).
[59] *Id.* at 1138:25-1140:14.
[60] ECF No. 9737-1 at 48-57; ECF No. 9914 at 154-160.
[61] Ballman Rep. at 18-19, 29, ECF No. 9914, Ex. 147.
[62] Diette Hr'g Tr. at 1102:13-18.
[63] ECF No. 9914 at 167 (PSC's Response) (*citing* William A. Oleckno, *Epidemiology: Concepts and Methods* at 189 (2008), ECF No. 9914, Ex. 143).
[64] McTiernan Hr'g Tr. at 781:8-25 ("Biological plausibility refers to does an association make sense? Is there some plausible pathway through which exposure to these products can cause cancer?"); Saenz Hr'g Tr. at 1827:13-1828:3 ("[I]t does not need to be proof positive for there to be biologic plausibility… It can just be that there is enough science to make sense"); Diette Hr'g Tr. at 1180:18-25.
[65] *See, e.g.*, McTiernan Hr'g Tr. at 735:8-23; Clarke-Pearson Hr'g Tr. at 1546:9-10.

studies and combined analyses are the best available evidence. As exemplified by J&J's expert reports, how these studies are prioritized, if at all, can affect and drive the conclusion reached.[66]

For this reason, J&J wrongly asserts that it is "fundamental[,]" "long standing[,]" and "well-established"[67] that there is a "hierarchy of evidence" that identifies cohort studies – favored by J&J – as categorically more reliable than case-control studies. The *Reference Manual on Scientific Evidence* and other reliable authorities disagree.[68] To the contrary, it is fundamental that all observational studies are on the same strata of evidentiary reliability.[69] Even J&J's expert, Dr. Diette, conceded that there is ***not*** a formal hierarchy and agreed that case-control and cohort studies "do belong in the same strata."[70]

Consistent with this principle, Dr. McTiernan explained that all observational studies "give useful information" but "can have benefits, strengths, and they can

[66] ECF No. 9737-1 at 29-37.
[67] ECF No. 9736 at 9-12; *see also* ECF No. 9736 (J&J's Mot. to Exclude) at 9-26; ECF No. 9914 (PSC's Response) at 96-131; *See also* ECF No. 9737-1 at 17-37.
[68] ECF Doc. No. 9914 at 114-131; *Reference Manual on Scientific Evidence*, Federal Judicial Center, Third Edition (2011) at 723-24 (hereinafter "*Ref. Man.*").
[69] *Ref. Man.* at 723-24; *see also In re Roundup Prod. Liab. Litig.*, 390 F. Supp. 3d 1102 (N.D. Cal. 2018) ("concerns about recall bias do not demand that a reliable expert opinion meaningfully discount the body of case control studies when assessing causation.").
[70] Diette Hr'g Tr. at 1126:18-1128:7.

have weaknesses."[71] Accordingly, the proper methodology is not to "place any hierarchy" on observational studies by design but, rather, to evaluate the strengths and weaknesses of each individual study to determine its relevance and importance.[72] That is precisely what the PSC's experts did.

For example, Dr. McTiernan explained that case-control studies are very effective in assessing diseases – particularly rare ones like ovarian cancer – because they are focused on the specific exposure of interest, but can be subject to "recall bias."[73] Conversely, while cohort studies are prospective and not subject to recall bias, they are not as effective in studying rare cancers because they are not designed to study individual exposures or diseases.[74] As a result, cohort studies may not have enough cases to attain statistical power and may not be sufficiently long to account for latency.[75] Cohort studies also may not adequately collect information on

[71] McTiernan Hr'g Tr. at 736:4-25, 764:24-765:22, 776:1-7; *see also* Gordis, *Epidemiology* at 266-270 (describing confounding variables).
[72] McTiernan Hr'g Tr. at 736:4-739:24.
[73] *See generally id.* at 731:21-739:24; *see also* McTiernan Hr'g Slides at 21. In *Epidemiology*, a textbook Dr. Diette conceded is authoritative (Diette Hr'g Tr. at 1133:15-23), Dr. Gordis observed "[a]lthough a potential for recall bias is self-evident in case control studies, in point of fact, ***few actual examples demonstrate that recall bias has, in fact, been a major problem in case-control studies*** and has led to erroneous conclusions regarding associations." *Id.* at 199 (emphasis added).
[74] McTiernan Hr'g Tr. at 737:1-739:24.
[75] *Id.* at 737:1-739:24, 762:24-776:12; McTiernan Hr'g Slides at 18-20.

exposure period or usage patterns, raising a concern for misclassification bias, which attenuates a true association.[76]

Accordingly, while J&J and its experts' preference may be to systematically place more weight on the cohort studies at issue here, this is not a "fundamental" epidemiological principle and would be improper methodology. To the contrary, it is proper that the PSC's experts considered and weighed all studies. This weighing of evidence by competing experts is not an appropriate basis for exclusion.

b. J&J's Significance Testing is Not a Proper Methodology

J&J's experts also erroneously imply that significance testing is a fundamental epidemiologic principle that the PSC's experts did not follow.[77] While, Dr. Diette conceded statistical significance is not the only measure of consistency,[78] he also testified that P-values and significance testing are required.[79] Dr. Diette is wrong.

Contemporaneous with the *Daubert* Hearing, the *New England Journal of Medicine* ("NEJM") issued its "New Guidelines for Statistical Reporting in the Journal," limiting the use of P-values:

> Journal editors and statistical consultants have become increasingly concerned about the overuse and misinterpretation of significance testing and P values in the medical literature. Along with their strengths,

[76] McTiernan Hr'g Tr. at 948:23-950:12; McTiernan Hr'g Slides at 18-20. For a fulsome discussion of how these biases can affect risk in both directions, *see* Gordis, *Epidemiology* at 264-266.
[77] ECF No. 9737-1 at 17-28; ECF No. 9914 at 94-98.
[78] Diette Hr'g Tr. at 1138:25-1140:14.
[79] *Id.* at 1154:2-1157:22.

P values are subject to inherent weaknesses, as summarized in recent publications from the American Statistical Association.[80]

Thus, the PSC's experts properly considered all epidemiological data, including statistically significant and non-statistically significant data, in evaluating consistency. The NEJM guidelines also demonstrate that J&J's contrary position on this issue is, in fact, a minority view.

C. THE OBSERVATIONAL EVIDENCE SUPPORTS A CAUSAL ASSOCIATION BETWEEN TPP AND OVARIAN CANCER

The epidemiologic evidence relied on by the PSC's experts supports a causal association between TPP and ovarian cancer.

1. Human observational studies support the PSC's experts' opinions

a. Case-control and cohort studies

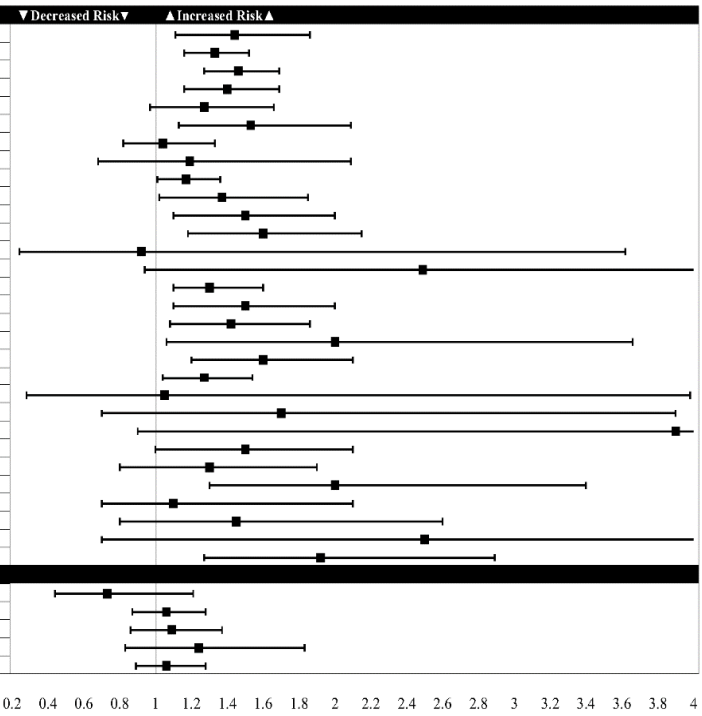
As the Court heard during the hearing, dozens of individual studies over the past four decades addressed the association between TPP and ovarian cancer. These studies, from multiple researchers and countries, include over two-dozen published case-control studies and five published studies from three cohorts.[81] In their totality, they show a statistically significant increased risk with evidence of a dose-response:

- **Association and Consistency of Association:** The demonstrated association and consistency of association between TPP and ovarian cancer is

[80] Harrington, et. al, *New Guidelines for Statistical Reporting in the Journal*, 381 N.E.J.M. 285-286, at 285 (Jul. 18, 2019), attached as **PD Exhibit 5**.
[81] Women's Health Initiative (WHI); Nurses Heath Study (NHS); Sister Study (SS).

summarized in the below forest plot produced by Dr. McTiernan[82] and used throughout the *Daubert* Hearing.

Case-Control Study	Natl	Cases	Ctrls	Pop	DR	RR	CI L	CI U
Schildkraut 2016	US	584	745	Pop.	Yes	1.44	1.11	1.86
Cramer 2016	US	2041	2100	Pop.	Yes	1.33	1.16	1.52
Wu 2015	US	1791	2391	Pop.	Yes	1.46	1.27	1.69
Kurta 2012	US	902	1802	Pop.	N/A	1.4	1.16	1.69
Rosenblatt 2011	US	812	1313	Pop.	No	1.27	0.97	1.66
Wu 2009	US	609	688	Pop.	Yes	1.53	1.13	2.09
Moorman 2009 (white)	US	1114	1086	Pop.	N/A	1.04	0.82	1.33
Moorman 2009 (black)	US	1114	1086	Pop.	N/A	1.19	0.68	2.09
Merritt 2008	Aus	1576	1509	Pop.	Yes	1.17	1.01	1.36
Mills 2004	US	256	1122	Pop.	No	1.37	1.02	1.85
Ness 2000	US	767	1367	Pop.	Incpl	1.5	1.1	2.0
Cramer 1999	US	563	523	Pop.	Yes	1.6	1.18	2.15
Wong 1999	US	499	755	Hosp.	Incpl	0.92	0.24	3.62
Godard 1998	Can	170	170	Pop.	N/A	2.49	0.94	6.58
Green 1997	Aus	824	855	Pop.	Incpl	1.3	1.1	1.6
Cook 1997	US	313	422	Pop.	No	1.5	1.1	2.0[1]
Chang 1997	Can	450	564	Pop.	No	1.42	1.08	1.86
Shushan 1996	Isr	200	408	Pop.	N/A	2	1.06[2]	3.66[2]
Cramer 1995	US	450	454	Pop.	N/A	1.6	1.2	2.1
Purdie 1995	Aus	824	860	Pop.	N/A	1.27	1.04	1.54
Tzonou 1993	Gre	189	200	Hosp.	N/A	1.05	0.28	3.98
Rosenblatt 1992	US	77	46	Hosp.	Yes	1.7	0.7	3.9
Chen 1992	Chn	112	224	Pop.	N/A	3.9	0.9	10.63
Harlow 1992	US	235	239	Pop.	Yes	1.5	1.0	2.1
Booth 1989 (daily)	UK	235	451	Hosp.	Yes	1.3	0.8	1.9[1]
Booth 1989 (weekly)	UK	235	451	Hosp.	Yes	2.0	1.3	3.4
Harlow 1989	US	116	158	Pop.	N/A	1.1	0.7	2.1
Whittemore 1988	US	188	539	H&P	Yes	1.45	0.81[1]	2.60[1]
Hartge 1983	US	135	171	Hosp.	N/A	2.5	0.7	10.0
Cramer 1982	US	215	215	Pop.	N/A	1.92	1.27	2.89
Cohort Studies	**Natl**	**Cases**	**Non**	**Flw Up**	**DR**	**RR**	**CI L**	**CI U**
Gonzalez (2016)	US	154	41,500	6.6	N/A	0.73	0.44	1.2[1]
Houghton (2014)	US	429	61,147	12.4	Incpl	1.06	0.87	1.28
Gertig (2000)	US	307	78,323	N/A	Incpl	1.09	0.86	1.37
Gates (2008)	US	210	600	N/A	Yes	1.24	0.83	1.83
Gates (2010)	US	797	78,323?	N/A	N/A	1.06	0.89	1.28



[1] Corrected data-point from study text (report figure: Cook 1997 CI Upper 2.3; Gonzalez CI Upper 1.21; Booth 1989 CI Upper 1.0; Whittemore CI p=0.06).
[2] Corrected data-point from defense expert report(s) (report figure: p=0.04).

Dr. McTiernan testified that the studies, regardless of design, show a "remarkably consistent [risk] because you could see that almost all of those

[82] McTiernan Hr'g Slides at 12 (plot). As Dr. McTiernan explained, the key data for assessing association and consistency are: (1) RR, which is the "most important statistic" and "refers to what is the risk in exposed individuals compared to somebody who is not exposed," and "tells us the strength, how large was the association," (McTiernan Hr'g Tr. at 742:17-743:6); (2) the number of ovarian cancer cases in each study, which she called "the critical number" and the "key variable" to determine power of the study to detect a risk (*id.* at 733:14-22, 741:7-742:2, 748:24-749); and (3) CI's, which describe the likely distribution of results if the "universe" of patients were studied, with narrow confidence intervals being "more precise" (*id.* at 743:7-744:24). Dr. McTiernan also noted that non-statistical significance, based on a p=.05, was noted by CI's that cross 1.0, which she explained is not the metric for determining association and consistency across studies in the epidemiologic and statistical community. *Id.* at 754:2-21, 749:11-752:25, 934:16-935:24; ECF No. 9737-1 at 7-47; ECF No. 9914 at 91-131; Wasserstein (2016) at 129; Amrhein (2019); *see supra* n. 54

relative risk data points are to the right of the [1.0 RR] line."[83] She also noted that the risk of serous epithelial ovarian cancer is also remarkably consistent.[84]

- **Strength:** The association found in the studies also meets the strength guideline. While the significant and non-significant risk estimates for each case-control study were in the 10-60% range, each of the eight meta-analyses and the sole pooled study showed a statistically significant 22-33% increased risk for ovarian cancer. Dr. McTiernan testified that based on the totality of the evidence, viewed in the context of the strength and consistency of the study results, the evidence "strongly supports a causal association."[85]

- **Dose-Response:** Dr. McTiernan assessed in her report that "[m]any of the 28 case control studies found evidence of a dose-response effect…… Thus, the studies that accurately determined use of talcum powder products revealed evidence of dose-response effects. When present, the finding of a biologic gradient/dose-response is helpful in determining causation. The findings within the study data, particularly meta-analyses and the pooled analysis, thus, supports my causal analysis and I placed significant weight on this factor."[86] She additionally noted during the hearing that "[l]ooking over all, there is a dose-response particularly because the meta-analysis and the pooled analysis saw that clearly."[87] This evidence of dose-response supports causation.

b. Neither chance, bias, nor confounding affect the reliability of the observed association

The PSC's experts sufficiently considered the potential effects of bias, confounding, chance, statistical power, and latency on the results of the observational studies – whether positively or negatively.

[83] McTiernan Hr'g Tr. at 752:2-16.
[84] *Id.* at 753:1-754:7.
[85] McTiernan Rep. at 64.
[86] *Id.* at 65-66.
[87] McTiernan Hr'g Tr. at 798:11-13.

Dr. McTiernan found, as have others,[88] that the case control studies are reliable because the risks of chance, confounding, and recall bias were low. She explained that replication of studies reduced the risks of chance[89] and unintentional confounding[90] and recall bias was unlikely since the observed association was differentially associated with serous ovarian cancer, a subtype of epithelial ovarian cancer.[91]

By contrast, Dr. McTiernan explained that cohort studies, including the WHI for which she was the Project Director, suffered from serious design and implementation flaws.[92] The cohort studies were not designed to look for the causes of ovarian cancer, were not powered to assess the risk of ovarian cancer (i.e. there were not enough cases in the cohort), were not long enough to account for latency, and suffered from significant "non-differential misclassification bias" because of the way the questionnaires were administered.[93]

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[88] *See*, *e.g.*, Schildkraut, et al., *Association Between Body Powder Use and Ovarian Cancer: The African American Epidemiology Study (AACES)*, 25 Cancer Epidemiology Biomarkers Prev. 1411, 1416 (2016), ECF No. 9914, Ex. 8; Penninkilampi, et al., *Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis*, 29 Epidemiology 41, 47 (2018), ECF No. 9914, Ex. 62; Health Canada (2018) at 28, ECF No. 9914, Ex. 56; IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 93: Carbon Black, Titanium Dioxide and Talc (2010) at 409, ECF No. 9914, Ex. 57.
[89] McTiernan Hr'g Tr. at 752:17-752:25, 762:10-762:23.
[90] *Id.* at 758:5-760:14.
[91] *Id.* at 772:2-776:7. *See also* discussion of Taher (2019) and Penninkilampi (2018) below.
[92] McTiernan Hr'g Tr. at 767:10-771:10.
[93] *See* McTiernan Hr'g Slides at 18-20; McTiernan Hr'g Tr. at 762:24-776:12.

2. J&J's critiques of the observational data are unavailing, and go to weight, not admissibility

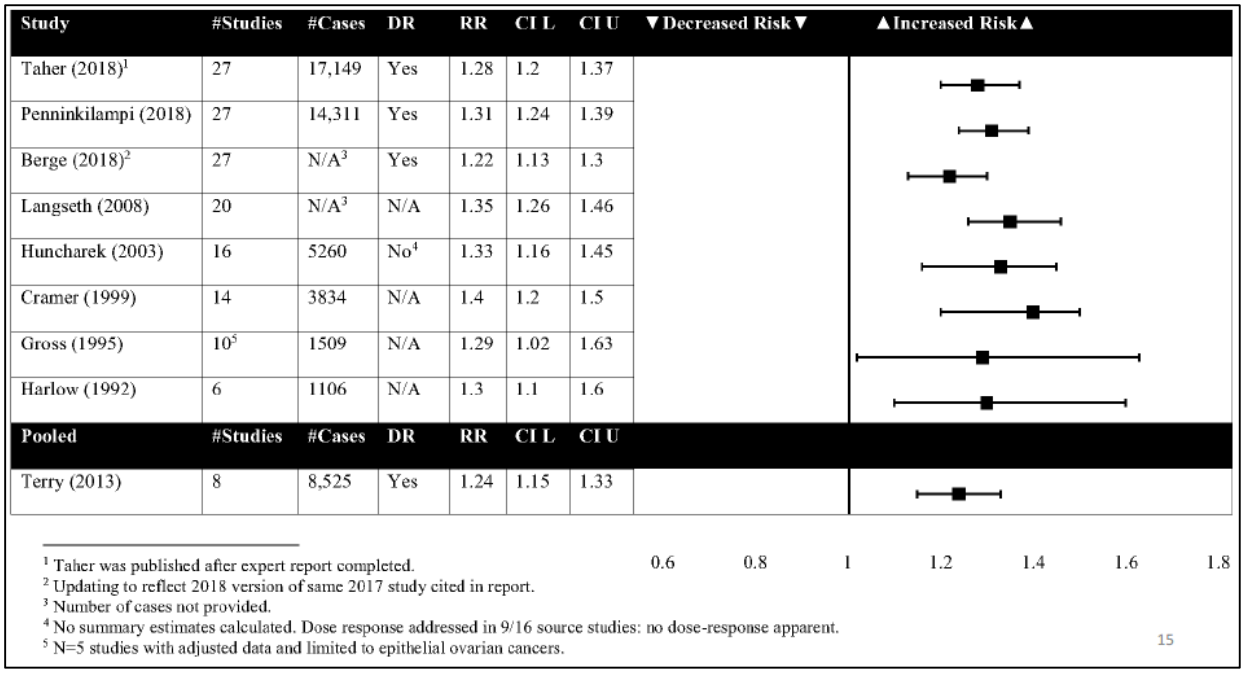
J&J critiques the observational data as being inconsistent and the result of recall bias and confounding. The following demonstrates that J&J's critiques are issues of weight for a jury, not admissibility:

- **Schildkraut (2016):** J&J attempts to undermine the case-control studies due to recall bias. This is pure speculation. J&J's experts' reliance on Schildkraut (2016) to illustrate that recall bias drives the results in the case-control studies is misplaced. Apart from the authors' conclusion that there is a 44% increased risk in epithelial ovarian cancer (specificity), evidence of dose-response; and that inflammation is a biologically plausible mechanism for the association,[94] the authors specifically addressed recall bias and concluded that the evidence "do[es] ***not support*** that recall bias alone" accounts for "the association between body powder use and EOC."[95]
- **Cramer/Gabriel (2019):** J&J also raises the specter that unadjusted-for confounding infected the results of the studies. To be a confounder, the variable must be both a cause of ovarian cancer and it must be differentially correlated with TPP use.[96] Relying on Gonzalez, et al., J&J pressed douching as a possible confounding cause. However, Dr. Diette could not say to a reasonable degree of medical certainly that douching as described in Gonzalez is in fact a confounding factor.[97] A recently accepted study for publication clearly demonstrates that douching is not a confounder.[98] The study notes that

[94] Schildkraut (2016) at 1416 ("The dose–response observed for duration of genital powder use provides further evidence for the relationship between genital powder and overall EOC risk. Our data suggest that the increased risk due to use of genital powder applies to both serous and non-serous histologic subtypes of EOC").
[95] *Id.*
[96] For a discussion of confounding, *see* Gordis, *Epidemiology* at 266-270.
[97] Diette Hr'g Tr. at 1177:3-16.
[98] Gabriel, et al., *Douching, Talc Use, and Risk for Ovarian Cancer and Conditions Related to Genital Tract Inflammation*, Cancer Epidemiology, Biomarkers, and Prevention (accepted for publication August 16, 2019), attached as **PD Exhibit 6**.

"douching is not an independent risk factor for ovarian cancer" and concludes that douching may actually enhance the carcinogenic properties of talc.[99]

- **Meta-Analyses and Pooled Analysis:** There have been eight meta-analyses and one pooled analysis involving TPP and the risk of ovarian cancer. These composite studies are intended to combine individual studies in a way that allows epidemiologists to see what the "literature looks like overall."[100] To illustrate her findings, Dr. McTiernan placed these studies on a forest plot:[101]



Study	#Studies	#Cases	DR	RR	CI L	CI U
Taher (2018)[1]	27	17,149	Yes	1.28	1.2	1.37
Penninkilampi (2018)	27	14,311	Yes	1.31	1.24	1.39
Berge (2018)[2]	27	N/A[3]	Yes	1.22	1.13	1.3
Langseth (2008)	20	N/A[3]	N/A	1.35	1.26	1.46
Huncharek (2003)	16	5260	No[4]	1.33	1.16	1.45
Cramer (1999)	14	3834	N/A	1.4	1.2	1.5
Gross (1995)	10[5]	1509	N/A	1.29	1.02	1.63
Harlow (1992)	6	1106	N/A	1.3	1.1	1.6
Pooled	**#Studies**	**#Cases**	**DR**	**RR**	**CI L**	**CI U**
Terry (2013)	8	8,525	Yes	1.24	1.15	1.33

[1] Taher was published after expert report completed.
[2] Updating to reflect 2018 version of same 2017 study cited in report.
[3] Number of cases not provided.
[4] No summary estimates calculated. Dose response addressed in 9/16 source studies: no dose-response apparent.
[5] N=5 studies with adjusted data and limited to epithelial ovarian cancers.

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All of the studies showed a consistent 22-31% increased risk of ovarian cancer with TPP. Four of the studies (Taher (2019), Penninkilampi (2018), Berge (2018), and Terry (2013)) were discussed extensively at the *Daubert* Hearing.

- **Taher (2019)**:[102] In December 2018, Health Canada published a Health Assessment for public comment,[103] and commissioned the Taher study, a draft of which was used at the hearing.[104] Subsequently, Taher was published in the journal *Reproductive Toxicology*.[105] The conclusion that TPP is a possible

[99] *Id.* at 9.
[100] McTiernan Hr'g Tr. at 733:23-735:3.
[101] McTiernan Hr'g Slides at 15.
[102] Taher (2019) at 88-101.
[103] Health Canada (2018) at 1-2.
[104] Taher (2019) at 99.
[105] *Id.* at 88.

cause of ovarian cancer remains the same as in the unpublished version. The published version also concluded: (1) their meta-analysis showed ***association,*** a statistically significant 28% increased risk across studies; (2) they showed ***biologic plausibility*** since *in vitro* and *in vivo* studies support migration, and "irritation, followed by oxidative stress and chronic inflammation, may be involved in local carcinogenic effects of talc in the ovaries"; (3) there was evidence of ***dose-response*** since the risk for high talc use was greater than medium and low use talc use; (4) the risk was correlated with ***specific*** types of ovarian cancer; and (5) the study findings assumed that the talc was asbestos-free.[106] Moreover, Taher agreed that there were significant shortcomings in the cohort studies which they discussed at length, including their relatively short study follow-up, lack of power, and potential for differential misclassification bias – all attenuating factors.[107]

- **Penninkilampi (2018)**:[108] Consistent with other meta-analyses, Penninkilampi reported a statistically significant 31% increased risk of ovarian cancer with TPP. The authors' meta-analysis of the cohort studies also showed a statistically significant 25% increased risk in serous ovarian cancer. The authors observed a consistent association across studies, evidence of a greater risk after 10 years, *i.e.*, dose-response, and that case control studies are "preferred [studies] in the investigation between talc use and ovarian cancer" to cohort studies. They opined that: "the confirmation of an association in cohort studies between perineal tac use and serous invasive ovarian cancer is suggestive of a causal association."[109]
- **Berge (2018):**[110] In the Berge meta-analysis, the authors found a statistically significant 26% increased risk, particularly with serous ovarian cancer. Their finding detracted from the hypothesis that recall bias was "an explanation of the findings of the case control studies, as this type of bias would likely operate for all histological types of the disease."[111] Additionally, they found a weak but statistically significant dose-response with serous ovarian cancer.

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[106] *Id.* at 94.
[107] *Id.* at 97.
[108] Penninkilampi (2018) at 47.
[109] *Id.*
[110] Berge, et al., *Genital Use of Talc and Risk of Ovarian cancer: a Meta-Analysis,* 27 European J. Cancer Prev. 248 (2018), ECF No. 9914, Ex. 61.
[111] Berge (2018) at 243.

- **Terry (2013):**[112] Terry was a pooled analysis using resources and data from the Ovarian Cancer Association Consortium. Terry concluded that genital powder use was "associated with a modest" statistically significant 24% increased risk of ovarian cancer. Dr. McTiernan opined that this pooled analysis provides strong evidence that genital TPP use causes ovarian cancer.[113] When the authors looked at frequency and duration of use, they found increased risks of ovarian cancer with increasing dose, evidencing a clear dose-response relationship.[114]

3. The regulatory assessments support the PSC's experts' opinions

To date, two regulatory bodies have performed a systematic analysis of the TPP-ovarian cancer question: IARC in 2006 (reported in 2010) and Health Canada in 2018. While these analyses took place twelve years apart, and IARC's did not have the benefit of later studies Health Canada had the opportunity to consider, the underlying conclusions of both support the opinions of the PSC's experts.

- **IARC**: As of 2006, IARC found the case-control studies "remarkably consistent," and noted it was "unlikely that [recall] bias could explain the set of consistent findings that stretch over two decades"[115] and the number of studies across countries and cultural contexts "reduces the likelihood of a hidden confounder."[116] With respect to chance, "it seemed very unlikely to be responsible for the consistent pattern of excess risks."[117] However, because of the lack of available biologic data in 2006, IARC categorized perineal use of talc without asbestiform fibers only as possibly carcinogenic to humans (Group 2B).[118]

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[112] Terry, *et al., Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 85,25 Cases and 9,859 Controls,* 6 Cancer Prev. Research 811 (2013), ECF No. 9914, Ex. 50.
[113] McTiernan Rep. at 55; McTiernan Hr'g Tr. at 791:5-792:15, 889:3-15.
[114] McTiernan Rep. at 54.
[115] IARC (2010).
[116] *Id.* at 408-409.
[117] *Id.* at 409.
[118] *Id.* at 412.

- **Health Canada:** In December 2018, Health Canada issued its Bradford Hill assessment, reviewing the same epidemiologic and biologic evidence that the PSC's experts rely on, and, employed the same methods the PSC's experts performed.[119] Like the PSC's experts, Health Canada concluded the evidence "consistent with the Hill criteria, suggests a small but consistent statistically significant positive association between ovarian cancer and perineal exposure to talc. Further, available evidence are indicative of a causal effect."[120]

III. THE BIOLOGICAL PLAUSIBILITY OPINIONS OF THE PSC'S EXPERTS ARE ADMISSIBLE

J&J separately moved to exclude the PSC's experts' opinions regarding biological plausibility, notwithstanding the fact that it is only one aspect of the Hill Guidelines. According to J&J, the PSC's experts' biological plausibility opinions are inadmissible because they are not based on conclusive proof that TPP migrates from the perineum to the ovaries and fallopian tubes or that TPP causes neoplastic transformation.[121] As clarified during the hearing, biological plausibility does not require such exacting proof – something J&J's own experts conceded. The PSC's experts' biological plausibility opinions are the product of reliable methodology and sound science, and therefore, are admissible under Rule 702.

A. ALL EXPERTS AGREE, BIOLOGICAL PLAUSIBILITY DOES NOT REQUIRE "PROOF" OF MECHANISM

Although J&J would have this Court believe otherwise, the PSC is not tasked with proving biological plausibility.[122] Rather, biological plausibility asks whether,

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[119] Health Canada (2018) at 15-22.
[120] *Id.* at 21.
[121] *See* ECF No. 9736-1 at 4-5; *and* ECF No. 10036 at 16-17, 36.
[122] ECF No. 9890 at 5-9.

based on existing science, the alleged association between the causative agent and disease makes sense.[123] While biological plausibility is "helpful" to understanding causation, it is not required.[124] Nor must the precise proposed mechanism be proven.[125] Biological plausibility is satisfied if, based on current scientific knowledge and reasoning, "you determine a way in which th[e association] could happen,"[126] even if there is "robust debate in the scientific community" on the proposed mechanism.[127] "The fact that the mechanism remains unclear does not call the reliability of the opinion [of biological plausibility] into question."[128]

Despite this clear standard, J&J seeks to exclude the PSC's experts' opinions because "they cannot point to any evidence that talc moves through the body to the

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[123] Hill (1965) at 298; *Ref. Man.* at 604-05; *Milward v. Acuity Specialty Prod. Grp., Inc.*, 639 F.3d 11, 25 (1st Cir. 2011).

[124] Hill (1965) at 298; *In re Denture Cream Prod. Liab. Litig.*, 795 F. Supp. 2d 1345, 1356 (S.D. Fla. 2011) ("When mechanistic evidence is presented it can greatly strengthen a causal inference, but when it is absent it does not necessarily undermine the inference").

[125] *In re Abilify (Aripiprazole) Prod. Liab. Litig.*, 299 F. Supp. 3d 1291, 1308 (N.D. Fla. 2018) ("[A]n expert on biological plausibility need not definitively prove the biological means by which a drug acts in the body."); *Milward*, 639 F.3d at 25.

[126] McTiernan Hr'g Tr. at 781:18-782:4; *Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1319 n.23 (11th Cir. 1999) ("While scientific testimony need not be known to a certainty, *Daubert* does require that assertions be derived from scientific knowledge."); *Milward*, 639 F.3d at 25.

[127] *In re Neurontin Mktg., Sales Practices, & Prod. Liab. Litig.*, 612 F. Supp. 2d 116, 149 (D. Mass. 2009).

[128] *In re Phenylpropanolamine (PPA) Prod. Liab. Litig.*, 289 F. Supp. 2d 1230, 1247 (W.D. Wash. 2003); *see also In re Fosamax Prod. Liab. Litig.*, 645 F. Supp. 2d 164, 183 (S.D.N.Y. 2009) ("That the mechanism remains unknown does not mean that the one proposed by the [expert] is not widely acceptable as plausible.").

ovaries in the way they propose – or that it causes the reactions they theorize."[129] In other words, J&J and its experts fault the PSC and their experts for failing to have studies that prove the mechanism.

But ***both sides'*** experts agree that biological plausibility does not require this level of proof. Dr. McTiernan testified "[b]iological plausibility refers to does an association make sense? Is there some plausible pathway through which exposure to these products can cause cancer?"[130] It is not the same as "biological proof and biological certainty."[131]

J&J's gynecologic oncology expert Dr. Saenz conceded as much, stating:

> [B]iological plausibility means that you are proposing a hypothesis, and based on that hypothesis, the concept that whatever it is you are proposing could actually happen is substantiated by some science that has been done in the field…[***I]t does not need to be proof positive for there to be biological plausibility, nor does it need to be an exact representation of whatever is your hypothesis. It can just be that there is enough science to make sense and extend it***.[132]

J&J's molecular expert Dr. Neel similarly admitted that all that is needed is "some credible scientific evidence supporting the hypothesis."[133] But, that "doesn't mean the evidence covers everything."[134] As Dr. Saenz further explained, even

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[129] ECF No. 10036 at 7, 18.
[130] McTiernan Hr'g Tr. at 781:8-17.
[131] *Id.* at 781:18-20.
[132] Saenz Hr'g Tr. at 1827:15-1828:3 (emphasis added).
[133] Neel Hr'g Tr. at 295:12-15.
[134] *Id.* at 318:14-20; *see also* Diette Hr'g Tr. at 1180:22-25 (biological plausibility is "whether or not the association seen or suggested makes sense").

though the evidence may not be "an exact representation of whatever is your hypothesis," so long as the evidence is consistent with your hypothesis "to make sense," it can be "extend[ed]" to the hypothesis.[135] That is precisely what the PSC's experts have done. Despite J&J's assertions that something more is required, under the correct standard for biological plausibility (about which all experts agree), the PSC's experts provide admissible opinions on biological plausibility.[136]

B. THE BIOLOGICAL PLAUSIBILITY OPINIONS OF THE PSC'S EXPERTS ARE BASED ON RELIABLE EVIDENCE THAT SUPPORTS THE HYPOTHESIS

The PSC's experts have demonstrated with the support of reliable and credible scientific and medical evidence that it is biologically plausible that TPP can cause ovarian cancer because: (1) TPP gets to the ovaries, fallopian tubes, and peritoneal surfaces through the genital tract after being applied to the perineum and through the blood stream and lymphatic system after being inhaled; and (2) once there, TPP can induce chronic inflammation, oxidative stress, and reactive oxygen species (ROS), which can lead to malignant transformation and cancer.[137]

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[135] Saenz Hr'g Tr. at 1828:2-3.

[136] To the extent J&J's experts' opinions are based on an incorrect standard of biological plausibility, the opinions must be excluded. *See* ECF No. 9735-1.

[137] Clarke-Pearson Hr'g Tr. at 1696:21-1697:1 (testifying it is biologically plausible that TPP can reach the ovaries and once there, cause chronic inflammation); McTiernan Hr'g Tr. at 784:15-788:6 (testifying that based on the evidence TPP can get to the ovaries and fallopian tubes and once there, cause inflammation and malignant changes that lead to carcinogenesis); Carson Hr'g Tr. at 1259:13-1260:11, 1281:5-1284:20 (testifying to same); Clarke-Pearson Rep. at 7-8, 9; McTiernan Rep.

1. The PSC's experts' opinion that TPP can get to the ovaries, fallopian tubes and peritoneal surfaces is based on reliable science

The PSC's experts opine that the two pathways of exposure to TPP are through "[g]enital application and inhalation."[138] In briefing, J&J argues that this opinion is inadmissible because it is not based on a study that proves TPP migrates from the perineum through the body to the ovaries or fallopian tubes.[139] J&J's motion to exclude on this basis should be denied.

Biological plausibility does not require such a level of proof and therefore, the PSC's experts are not required to point to a specific study that proves TPP migrates from the perineum to the ovaries in order to opine on biological plausibility. Indeed, requiring such evidence is illogical when it does not exist for ethical reasons.[140] Dr.

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at 58-63; Carson Rep. at 8, 10; Smith Rep. at 16-18, 20, ECF No. 9914, Ex.11; Smith-Bindman Rep. at 35, 40, ECF No. 9914, Ex. 9; Wolf Rep. at 10-13, 15, ECF No. 9914, Ex. 14; Siemiatycki Rep. at 64-66, ECF No. 9914, Ex. 4.

[138] McTiernan Hr'g Tr. at 784:23-24; *see also id.* at 784:17-22 ("[I]t is an open system and there is evidence that genital application can migrate up through the genital tract. …[A]nd in addition, these substances can be inhaled and spread through the lymphatic system and circulatory system."); Clarke-Pearson Hr'g Tr. at 1530:17-22 ("[T]he mechanism is one of migration or ascension of the talcum powder from the perineum from the vulva through the vagina, cervix, uterus, and out the fallopian tube to rest on the ovary and peritoneum as the route of exposure. Inhalation is also a plausible mechanism for exposure."); Carson Hr'g Tr. at 1259:20-24 ("Talcum powder clearly migrates through the female reproductive tracts when it's applied to the perineum and exposes the ovaries. Inhalation of dust during those applications is a potential secondary route.").

[139] ECF No. 9736-1 at 4; ECF No. 10036 at 7.

[140] *See Schott v. I-Flow Corp.*, 696 F. Supp. 2d 898, 905 (S.D. Ohio 2010) (finding reliance on analogous studies for causation reasonable when most relevant studies "would be unethical" and therefore, finding it "unreasonable for Defendant to

Clarke-Pearson explained that "[t]here has been no experimental study to use talc in this setting of applying it, whether it's on the vulva, perineum, or vagina" because doing so "would be unethical at this point in time."[141] Accordingly, the PSC's experts rely on studies looking at whether it is possible that "particles of similar size to talc when applied to the genital tract can move up to the fallopian tubes and ovaries."[142] This evidence includes the rapid migration of carbon particles from the vagina to the fallopian tubes of women;[143] the migration of radioactive particles from the vagina to the fallopian tubes and ovaries of women within 24 hours of placement;[144] and, the presence of glove powder in the ovaries and fallopian tubes of women 24-48 hours after a vaginal examination.[145]

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clamour for such studies"); *Gess v. U.S.*, 991 F. Supp. 1332, 1339-40 (M.D. Ala. 1997) (expert could base mechanism opinion on animal studies where no conclusive clinical study was available because "[s]uch clinical study would be unethical under the tenets of modern medicine").

[141] Clarke-Pearson Hr'g Tr. at 1665:25-1666:10; McTiernan Hr'g Tr. at 786:5-9 ("The reasons the studies were not able to apply talc and see if that migrates, it wouldn't be ethical to do that. They chose other substances, and many of those were fertility type studies. They were able to do those tests and see what happens.").

[142] McTiernan Hr'g Tr. at 784:15-786:14; *see also* Carson Hr'g Tr. at 1279:2-1282:14; Carson Hr'g Slides at 12-13; Clarke-Pearson Hr'g Tr. at 1560:11-1562:17; Clarke-Pearson Hr'g Slides at 13-15; ECF No. 9890 at 10-21.

[143] Egli & Newton, *The Transport of Carbon Particles in the Human Female Reproductive Tract*, 12 Fert. & Ster. 151, 153 (1961), ECF No. 9914, Ex. 67.

[144] Venter & Iturralde, *Migration of a Particulate Radioactive Tracer from the Vagina to the Peritoneal Cavity and Ovaries*, 55 S. Afr. Medi. J. 917, 917-18 (1979), ECF No. 9914, Ex. 70.

[145] Sjosten et al., *Retrograde Migration of Glove Powder in the Human Female Genital Tract*, 19 Human Reprod. 991, 995 (2004), ECF No. 9914, Ex. 73.

The PSC's experts also rely on biological evidence that explains how upward movement of particulates occur. This includes the existence of the peristaltic pump in women which creates consistent contractions throughout a woman's menstrual cycle, transporting particulates up and down the female genital tract[146] and the occurrence of retrograde menstruation in up to 90% of women.[147]

Pathology studies further support the PSC's experts' opinions that TPP can migrate in the body by showing that talc and asbestos fibers actually have been found in the ovaries and surrounding lymph nodes of TPP users.[148] In these studies, the presence of talc and asbestos in the ovaries and lymph nodes "was highly correlated with whether the woman reported use of talc."[149] Accordingly, the PSC's experts'

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[146] Kunz et al., *The Uterine Peristaltic Pump Normal and Impeded Sperm Transport within the Female Genital Tract*, 49 The Fate of the Male Germ Cell 267-277 (1997), ECF No. 9914, Ex. 71; Kissler et al., *Uterine Contractility and Directed Sperm Transport Assessed by Hysterosalpingoscintigraphy (HSSG) and Intrauterine Pressure (IUP) Measurement*, 83 Acta Obstet. Gynecol. Scand. 369, 369-70 (2004), ECF No. 9890, Ex. 12; *see also* Henderson et al., *The Demonstration of the Migration of Talc from the Vagina and Posterior Uterus to the Ovary of the Rat*, 40 *Ev. Res.* 247, 247 (1986), ECF No. 9890, Ex. 17; Zervomanolakis et al., *Physiology of Upward Transport in the Human Female Genital Tract*, 1101 Ann. N.Y. Acad. Sci. 1, 1 (2007), ECF No. 9890, Ex. 14.

[147] Halme et al., *Retrograde Menstruation in Health Women and in Patients with Endometriosis*, 64 Obst. & Gyn. 151, 153 (1984), ECF No. 9914, Ex. 69; Blumenkrantz et al., *Retrograde Menstruation in Women Undergoing Chronic Peritoneal Dialysis*, 57 *Obst. & Gyn.* 667, 669 (1981), ECF No. 9890, Ex. 19.

[148] McTiernan Hr'g Tr. at 785:15-24; Clarke-Pearson Hr'g Tr. at 1562:15-17, 1564:3-14; ECF No. 9890 at 16-18 (discussing pathology evidence).

[149] McTiernan Hr'g Tr. at 785:19-24; *see also* Heller et al., *Asbestos Exposure and Ovarian Fiber Burden*, 29 *Am. J. Industrial Med.* 435, 436 (1996) ("Heller (1996-Asbestos)"), ECF No. 9890, Ex. 49 ("women with a positive exposure history had

opinion that TPP can migrate from the vagina to the ovaries and fallopian tubes is reliable, admissible, and well supported by the science.[150]

The evidence also supports the PSC's experts' opinions that inhalation is also a plausible route of exposure.[151] TPP particles are a respirable size that puts women at risk for inhalation exposure.[152] IARC recognizes that when inhaled, asbestos and

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asbestos detected in their ovaries more frequently"); McDonald et al., *Correlative polarizing light and scanning electron microscopy for the assessment of talc in pelvic region lymph nodes*, 43 Ultrastructural Pathology 13, 21 (2019), ECF No. 9890, Ex. 52 ("the level of talc in nodule tissue at least five times higher in those who used talc genitally").

[150] *See* Health Canada (2018) at 21 ("This evidence of retrograde transport supports the biological plausibility of the association between perineal talc application and ovarian exposure…."); Houghton et al., *Perineal Powder Use and Risk of Ovarian Cancer*, 106 JNCA 1, 1 (2014) ("Talc particulates from perineal application have been shown to migrate to the ovaries."), ECF No. 9914, Ex. 54; Langseth et al., *Perineal Use of Talc and Risk of Ovarian Cancer*, 62 J. Epidemiol. Comm. Health 358, 358 (2008) ("A majority of women experience retrograde menstruation; this suggests a mechanism by which talc can travel through the female reproductive tract to the ovaries."), ECF No. 9914, Ex. 5; April 1, 2014 FDA Response to Citizen's Petition, ECF No. 9914, Ex. 78; IARC Monograph on the Evaluation of Carcinogenic Risks to Humans, "Arsenic, Metals, Fibres, and Dusts Volume 100C A Review of Human Carcinogens," (2012) at 232, ECF No. 9914, Ex. 80; Sjosten (2004) at 991 ("Consequently, powder or any other potentially harmful substances that can migrate from the vagina should be avoided."); Venter (1979) ("If transit can take place so easily, it is probably the same for many chemical substances used for hygienic, cosmetic, or medicinal purposes, many of which may have potential carcinogenic or irritating properties.").

[151] ECF No. 9890 at 19-20. Importantly, J&J's experts did not provide any opinions regarding inhalation as a possible mechanism during the hearing. Dr. Saenz emphatically testified: "I've not studied, nor do I have an opinion on the inhalation of talc." Saenz Hr'g Tr. at 1877:10-15.

[152] Health Canada (2018) at 23; Steiling et al., *Principles for the Safety Evaluation of Cosmetic Powders*, 297 Tox. Letters 8, 12 (2018) (recognizing that loose powders, including baby powder, "could generate such a dust cloud or atmosphere during

fibrous talc are Group 1 carcinogens that can cause ovarian cancer.[153] IARC also acknowledges that asbestos and fibrous talc can migrate through the lymphatic system.[154] Accordingly, the evidence supports that "[t]here is a potential for inhalation exposure to talc powder during use…."[155]

2. J&J's critiques of the PSC's migration evidence go to weight, not admissibility

J&J does not argue that the science underlying the PSC's experts' opinions on migration is unreliable. Instead, J&J and its experts merely criticize the underlying studies for: only looking at migration from the vagina and not the perineum; not involving TPP; studying women that were lying down and not standing; and, failing to rule out contamination as the cause of talc and asbestos in the ovaries.[156] These arguments do not go to the admissibility of the PSC's experts' biological plausibility opinions. If anything, they go to the weight which is for a jury to determine.

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product handling or application, and therefore there is the potential for inhalation exposure"), ECF No. 9890, Ex. 54; Zelikoff Rep. at 15 (discussing particle size), ECF No. 9890, Ex. 24; *see* Carson Hr'g Tr. 1282:18-1283:3, 1369:20-24, 1370:10-1371:14 (testifying to a reasonable degree of certainty that talc fibers may be inhaled and reach the ovaries).

[153] IARC (2012) at 219, 232, 256, 280.

[154] *Id*. at 280.

[155] Health Canada (2018) at 22; *see also* Cramer et al., *Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc*, 110 *Obstetrics & Gynecology* 498 (2007) (finding talc in lymph nodes suggests exposure through inhalation), ECF No. 9914, Ex. 76; Wolf Rep. at 11; Clarke-Pearson Rep. at 8; Singh Rep. at 57-58, ECF No. 9914, Ex. 10; Kane Rep. at 14, ECF No. 9914, Ex. 15; Zelikoff Rep. at 14-17; Siemiatycki Rep. at 65.

[156] ECF No. 9736-1 at 18-40; ECF No. 10036 at 16-26.

First, critiques of the applicability of underlying science go to the weight of the opinions, which is not a basis for exclusion under Rule 702.[157] ***Second,*** the evidence of biological plausibility relied on by the PSC's experts need not be "an exact representative" of the hypothesis.[158] So long as the evidence is consistent, it can be "extend[ed]" to the hypothesis.[159] ***Third,*** J&J's own experts disagree with J&J's critique of the evidence and, instead, actually agree that TPP can easily enter the vagina from the perineum and therefore, studies showing migration of particles from the vagina upward are supportive of the PSC's opinions. Drs. Clarke- Pearson and McTiernan testified that because the vagina is open to the outside world, many "daily activities" such as walking, sexual intercourse, riding a bike, and using a tampon, can cause TPP to enter the vagina.[160]

J&J's gynecologic oncologist Dr. Saenz agrees. While she testified that her opinion on biological plausibility is that "there's never been a study" that shows

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[157] *See Leonard v. Stemtech Int'l Inc*, 834 F.3d 376 (3d Cir. 2016) ("Where there is a logical basis for an expert's opinion testimony, the credibility and weight of that testimony is to be determined by the jury, not the trial judge.") (quoting *Breidor v. Sears, Roebuck & Co.*, 722 F.2d 1134, 1138–39 (3d Cir. 1983)); *In re Tylenol (Acetaminophen) Mktg., Sales Practices & Prods. Liab. Litig.*, 2016 U.S. Dist. LEXIS 99176, at *35 and n.25 (E.D. Pa. Jul. 28, 2016) (critique of the applicability of underlying studies goes to weight and not reliability of opinion).

[158] Saenz Hr'g Tr. at 1827:22-1828:2.

[159] *Id.* at 1828:2-3.

[160] Clarke-Pearson Hr'g Tr. at 1562:18-1561:8; McTiernan Hr'g Tr. at 784:17-22 ("[I]t is an open system and there is evidence that genital application can migrate up through the genital tract); *see also* Wolf Dep. at 195:11-18, ECF No. 9914, Ex. 14.

particulate applied to the perineum can migrate to the ovaries, she agrees, consistent with the correct standard for biological plausibility, that "I think that probably could happen" and "I think that's possible."[161] Just as the PSC's experts testified, Dr. Saenz testified that TPP applied to the external genitals can get into the vagina by being "dragged in there" through, for example, intercourse or tampon use.[162] She also agrees that there are studies that show that once particulates are in the vagina, they can migrate to the ovaries: "Yes, I've seen some studies that have demonstrated that."[163] Dr. Saenz also does not disagree with IARC's conclusion that perineal application of TPP is the primary exposure source.[164]

J&J's own biologic plausibility expert, Dr. Michael Birrer,[165] previously testified to the same. He agrees that "[a]ny material – whether it be talc, heavy metals, asbestos, whatever – can migrate from the perineum to the ovaries through the reproductive tract. There's an anatomical conduit."[166] Accordingly, there is no

[161] Saenz Hr'g Tr. at 1868:7-1869:17.
[162] *Id.* at 1868:17-25, 1869:13-17, 1886:22-1887:5, 1897:16-23.
[163] *Id.* at 1869:18-22.
[164] *Id.* at 1877:22-1878:2. Because Dr. Saenz agrees the science supports migration under the correct standard for biological plausibility, her opinions to the contrary should be excluded. *See* Saenz Rep. at 8, 17-18, 27-28, ECF No. 9735, Ex. A.
[165] Birrer Rep. at 2 ("I was asked to address the biological plausibility of plaintiffs' theory that the use of cosmetic talcum can cause ovarian cancer."), ECF No. 9743, Ex. H.
[166] September 25, 2018 Deposition of Michael Birrer, M.D., *Brower, et al. v. Johnson & Johnson, Inc. et al.* at 96:22-97:8, ECF No. 9890, Ex. 41.

dispute among the parties' experts that TPP can enter the vagina from the perineum and once there, can migrate to the ovaries and fallopian tubes.

Fourth, the PSC's experts also have explained that the particles used in the studies on which they rely, while not TPP, are similar in size to TPP.[167] Other peer-reviewed authors agree.[168] They also have explained that the positions in which the women were placed in the underlying studies (*e.g.* lying down) are not unlike positions women exhibit in their daily lives.[169] Dr. Clarke-Pearson explained the obvious: "Women stand up; they sit down; they lie down."[170] Therefore, that the study subjects were lying down does not reflect circumstances that women applying TPP to their genitals would not similarly experience.

Finally, J&J's experts purely speculate that the presence of talc and asbestos in ovaries and surrounding lymph nodes in the pathology studies is due to contamination.[171] In fact, those study authors explicitly accounted for

[167] Carson Hr'g Tr. at 1280:22-4; Clarke-Pearson Hr'g Tr. at 1663:24-1664:1; McTiernan Hr'g Tr. at 785:1-4.
[168] Health Canada (2018) at 9 (noting that particles studied in Egli et al (1961) and Venter (1979) are "the same size as talc").
[169] Clarke-Pearson Hr'g Tr. at 1668:8-1669: 1670:10-1671:6 (during 24 hours before surgery women are not held in a horizontal position).
[170] *Id*. at 1664:8-19.
[171] Saenz Hr'g Tr. at 1832:10-1833:13 (testifying that she does "not know" how talc in Heller 1996 got to the ovaries); Saenz Rep. at 17 ("No one actually knows how the talc that is found in pathology samples gets there.").

contamination.[172] Additionally, a recent study relied on by the parties' experts addressed the contamination issue and still found talc in lymph nodes of women who used TPP.[173] The study authors concluded that their results confirmed "earlier observations that talc particles, from perineal exposure, can and do migrate to pelvic lymph nodes."[174]

The PSC's experts' opinions that TPP can get to the ovaries and fallopian tubes are supported by reliable methodology and science; therefore, they are admissible under Rule 702.

3. The PSC's experts' opinions regarding inflammation are based on reliable methodology and science

The PSC's experts opine that after reaching the ovaries, fallopian tubes and peritoneal surfaces, TPP causes chronic inflammation, which can lead to oxidative stress, DNA damage, and cancer.[175] These opinions are well-supported by the scientific and medical literature and explain the relevant epidemiology.[176]

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[172] *See* Heller et al. (1996-Asbestos) at 437; Heller et al., *The relationship between perineal cosmetic talc usage and ovarian talc particle burden*, 174 *Am. J. Obstet. Gynecol.* 1507, 1508 (1996), ECF No. 9890, Ex. 47.
[173] McDonald et al. (2019) at 15-16; ECF No. 9890 at 18 (discussing McDonald).
[174] McDonald et al. (2019) at 24.
[175] McTiernan Hr'g Tr. at 788:16-21, 790:13-17; Clarke-Pearson Hr'g Tr. at 1532:23-1531:4; Carson Hr'g Tr. at 1283:4-18.
[176] ECF No. 9890 at 21-31.

Reliable evidence demonstrates that talcum powder is known to cause chronic inflammation,[177] and asbestos and fibrous talc are known carcinogens that cause ovarian cancer.[178] "Chronic inflammation is induced by biological, chemical, and physical factors and is in turn associated with an increased risk of several human cancers."[179] Chronic inflammation plays a role in the initiation, growth, and metastasis of cancer by causing cell proliferation, oxidative stress, generation of ROS, and DNA damage.[180] Indeed, J&J's own experts agree with the inflammation cascade that leads to ovarian cancer. Dr. Neel testified that he agrees that inflammation can result in increased production of ROS, which can cause DNA damage and lead to genetic mutations.[181] He also agrees that oxidative stress plays a role in the development of cancer.[182] Talcum powder and asbestos have been shown to cause ROS, oxidative stress, and apoptosis, and to be genotoxic.[183]

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[177] *See* ECF No. 9890 at 21-31.
[178] *See* IARC (2012).
[179] Reuter et al., *Oxidative Stress, Inflammation, and Cancer: How are they Linked?* 49 *Free Radic Biol Med.* 1603, 1604 (2010), ECF No. 9890, Ex. 67.
[180] *See* ECF No. 9890 at 21-31, 46-51.
[181] Neel Hr'g Tr. at 330:15-18, 331:15-332:11.
[182] *Id.* at 332:24-333:8.
[183] Shukla, et al., *Alterations in Gene Expression in Human Mesothelial Cells Correlate with Mineral Pathogenicity*, 411 *American Journal of Respiratory Cell and Molecular Biology* 114 (2009), ECF No. 9914, Ex. 93; Buz'Zard and Lau, *Pycnogenol reduces Talc-induced Neoplastic Transformation in Human Ovarian Cell Cultures*, 21 Phytother. Res. 579 (2007), ECF No. 9914, Ex. 94; Akhtar et al., *Cytotoxicity and Apoptosis Induction by Nanoscale Talc Particles from Two Different Geographical Regions in Human Lung Epithelial Cells*, Environmental Tox 394 (2012), ECF No. 9914, Ex. 95; Akhtar et al., *The primary role of iron-*

Accordingly, reliable evidence demonstrates a biologically plausible mechanism by which TPP can cause ovarian cancer in women.[184]

4. J&J's arguments against inflammation as a mechanism do not provide a basis for exclusion under Rule 702

Like with the migration studies, J&J's experts fault the PSC's experts for relying on studies that do not prove TPP causes neoplastic transformation. Dr. Saenz admitted she ignored several primary studies relied on by the PSC's experts – Buz'Zard (2007), Shukla (2009), Akhtar (2010) and Akhtar (2012) – because "none of these studies actually showed malignant transformation" and "[s]o reading them I did not feel was important to my opinion…"[185]

Dr. Saenz's testimony reveals a weakness in her own opinions: how can you provide an opinion based on the totality of the evidence, when you have not in fact

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mediated lipid peroxidation in the differential cytotoxicity by two varieties of talc nanoparticles on A549 cells and lipid peroxidation inhibitory effect exerted by ascorbic acid, 24 Toxicology in Vitro 1139 (2010), ECF No. 9914, Ex. 96; Fletcher, et al., *Molecular Basis for Supporting the Association of Talcum Powder Use with Increased Risk of Ovarian Cancer*, Reproductive Sciences 1 (2019), ECF No. 9914, Ex. 97.

[184] Taher (2019) at 99 ("[W]e maintain our conclusion that talc is a possible cause of human cancer in humans based on the totality of evidence from multiple observational studies and plausible biological pathway involving chronic inflammation and oxidative stress."); Health Canada (2018) at 18 ("There is support for an association of inflammation and increased risk of ovarian cancer.").

[185] Saenz Hr'g Tr. at 1937:25-1938:11; *see also* Diette Hr'g Tr. at 1074:1-1075:14 (admitting that he did not consider five studies that "all have some bearing on inflammation"). The Buz'Zard study did in fact report talc-induced neoplastic transformation.

looked at the totality of the evidence? But more critically, Dr. Saenz's rejection of inflammation as a mechanism based on the lack of proof of neoplastic transformation is contrary to the proper burden of proof. Biological plausibility does not require the PSC to prove TPP results in neoplastic transformation. The PSC's experts need only point to evidence that supports chronic inflammation as a mechanism.

IV. THE OPINIONS OF DR. GHASSAN SAED REGARDING TPP, INFLAMMATION, AND OVARIAN CANCER ARE ADMISSIBLE

The PSC's expert, Dr. Ghassan Saed, has opined to a reasonable degree of scientific certainty that TPP is not an inert substance and, instead, induces an inflammatory response, alters the redox balance favoring a pro-oxidant state in normal and epithelial ovarian cancer cells, and does so while exhibiting a clear dose-response pattern.[186] It is Dr. Saed's opinion to a reasonable degree of scientific certainty that TPP exposure can cause ovarian cancer and worsen the prognosis for patients with ovarian cancer.[187] His opinions are based on his experience, training, and expertise, as well as a knowledge of the relevant scientific literature and his previous and ongoing research.[188] Dr. Saed's research and opinions are founded in sound methodology, based upon sufficient facts and data, are consistent with research conducted by other scientists, and establish a biologically plausible

[186] *See* Fletcher (2019) at 9; ECF No. 9875 at 12; Saed Rep. at 20, ECF No. 9890, Ex. 105; Saed Hr'g Tr. at 11:19-12:19; 56:2-10.
[187] *Id.* at 13:8-15.
[188] *Id.* at 58:25-59:6; Saed Rep. at 20-21.

mechanism by which TPP causes ovarian cancer. Dr. Saed's opinions and research satisfy the requirements of *Daubert* and are admissible.

A. DR. SAED UTILIZED RELIABLE PRINCIPLES AND METHODS IN CONDUCTING HIS RESEARCH AND FORMING HIS OPINIONS

In conducting his research, Dr. Saed employed methods that have been utilized for decades, generally accepted by the scientific community, and routinely applied within his laboratory. Dr. Saed has published over 50 peer-reviewed articles on oxidative stress and ovarian cancer, and his lab is focused on studying oxidative stress, inflammatory markers in the pathogenesis and causation of ovarian cancer. Dr. Saed used tests during his TPP research that have been used by his lab for decades.[189] "Everybody in cell biology and biochemistry uses them, everybody."[190]

Dr. Saed used commercially available ELISAs to measure redox protein levels and enzyme activities; the Greiss assay to measure nitrate/nitrite levels; RT-PCR to quantify RNA expression using redox gene specific primers; MTT assay for cell viability; Caspase 3 assays to measure apoptosis and programmed cell death, and Taqman-SNP genotyping to identify DNA point mutations induced by TPP treatment.[191] Each of the aforementioned markers employed by Dr. Saed have been

[189] Saed Hr'g Tr. at 20:4-12, 8:10-21, 20:4-17, 52:20-22, 55:1-14.
[190] *Id.* at 45:10-12.
[191] *See* Fletcher (2019) at 2-3; Saed Hr'g Tr. at 44:16-21.

generally accepted by the scientific community.[192] In fact, J&J's own experts acknowledged that the methods utilized by Dr. Saed have been peer-reviewed and published.[193]

B. THE PRINCIPLES AND METHODS EMPLOYED BY DR. SAED WERE RELIABLY APPLIED

The principles and methods employed by Dr. Saed were reliably applied. He used DMSO because it is an organic solvent commonly used in research studies and is a solvent that has been generally accepted by the research community. He chose doses for his research based upon similar doses that were used in published literature.[194] Dr. Saed employed a method of testing in triplicate that he believed to be more powerful than simply dividing a single cell into three plates. Significantly, Dr. Saed and others have previously published in peer-reviewed journals employing the method of triplicate that was employed during his TPP research.[195]

Dr. Saed chose three different ovarian cancer cell lines along with one normal primary ovarian epithelial cell, one normal epithelial fallopian tube cell and a normal non-epithelial cell for control.[196] As documented in Dr. Saed's laboratory notebooks, he exposed both cancer cell lines and normal cells to TPP for 72 hours. He chose

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[192] Saed Hr'g Tr. at 53:3-54:2, 55:1-14.
[193] *See* Birrer Dep. at 359:18-361:5 (confirming that not only the dosages but testing used by Dr. Saed's testing has been peer-reviewed and published).
[194] Saed Hr'g Tr. at 49:12-50:4, 50:7-16.
[195] *Id.* at 51:2-13, 52:1-15.
[196] *Id*. at 59:18-24.

those cell lines not only because he had experience and had published in peer reviewed journals using those cell lines in the past, but because others also have published using similar cell lines. His results were peer reviewed and published in *Reproductive Sciences.*[197]

All data generated during Dr. Saed's research is correct.[198] The data was captured electronically by computerized instruments and transferred from the instruments to Excel spreadsheets in the laboratory computers. None of the data is entered manually. The formulas used during the research are standard formulas used not just by Dr. Saed and his laboratory, but routinely by others in the industry and, in most instances, provided by the manufacturer of the test kit.[199]

As Dr. Saed testified, although there were transcription errors in manuscripts, those errors were corrected by him at the final editing stage.[200] Importantly, the final manuscript that was accepted by *Reproductive Sciences* and published in February 2019 contained no errors and accurately reflected the 72 hours of exposure relied upon by Dr. Saed in forming his opinions. J&J's own expert, Dr. Neel, testified that it is not uncommon for draft manuscripts to contain errors at the time of

[197] *Id.* at 18:4-23.
[198] *Id*. at 29:6-12.
[199] *Id*. at 19:16-23, 20:23-21:5, 21:8-11; 26:1-19, 27:14-20.
[200] *Id*. at 38:23-39:2.

submission.[201] At best, J&J's challenges in this regard go to the overall credibility of Dr. Saed, an issue best left for the jury.[202]

C. THE OPINIONS EXPRESSED BY DR. SAED ARE BASED UPON SUFFICIENT FACTS AND DATA

The opinions expressed by Dr. Saed are based upon sufficient facts and data. As an initial matter, the research done by Dr. Saed was reviewed by at least 20 independent expert peer reviewers.[203] The review process was not something that Dr. Saed took lightly. Where the sufficiency of his findings was questioned, Dr. Saed took the necessary steps to address the issue. For example, when Reviewer No. 2 from *Gynecologic Oncology* commented that Dr. Saed's work would be enhanced by transformation evidence, Dr. Saed performed the necessary studies and amended his manuscript prior to submission to *Reproductive Sciences* so that it included the results of his cell proliferation and apoptosis testing.[204]

As established by Dr. Saed during the *Daubert* Hearing, there were a multitude of tests that could have been used when conducting his experiments, but there was not a need to run every available experiment in order to form his opinions. Instead, Dr. Saed chose specific tests because they were well-established and his lab

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[201] Neel Hr'g Tr. at 364:1-13.

[202] Dr. Saed confirmed that missing pages and whiteout contained in the lab notebooks have no substantive effect on the results of his research. *See* Saed Hr'g Tr. at 35:5-9, 38:2-7.

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[204] Saed Hr'g Tr. at 73:13-74:10.

had routinely used them in the past.[205] To the extent J&J challenges the sufficiency of performing some but not all tests contained in Dr. Saed's budget document, it is only J&J and its experts who have lodged any such challenges. Not a single expert peer reviewer, including those from *Gynecologic Oncology*, questioned the methods employed by Dr. Saed.

Lastly, Dr. Saed was not required and did not need to conduct animal or human studies to support his findings. As Dr. Saed testified, *in vitro* studies are the gold standard for determining mechanism of action.[206] As J&J's expert, Dr. Brooke Mossman, recognized in her peer reviewed publication: "*in vitro* studies have been used historically to compare the effects of different types of minerals on cells or organ (explant) cultures." Dr. Mossman further stated that "*in vitro* studies have helped to establish mechanisms of fiber carcinogenesis and differentiated between responses to asbestos fibers and nonasbestiform particles."[207]

In the end, J&J has offered no credible evidence to undercut the methods applied by Dr. Saed or the facts and data relied upon in forming his opinions.[208] In

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[205] *Id*. at 54:19-55:4.
[206] *Id*. at 14:7-10.
[207] Mossman, *Assessment of the Pathogenic Potential of Asbestiform vs. Nonasbestiform Particulates (Cleavage Fragments) in In Vitro (Cell or Organ Culture) Models and Bioassays*, Reg. Tox. Pharm. 2008;52 (Supl.1): S200–3 (2007), attached as **PD Exhibit 7**.
[208] J&J's claim that Dr. Saed failed to provide adequate disclosures does not diminish the methods employed by Dr. Saed or the results of his research. Any issues related to the adequacy of disclosures goes to the expert's credibility, not admissibility.

contrast, independent expert peer review of Dr. Saed's work and several similar peer reviewed publications[209] bolster the work and opinions of Dr. Saed.

V. J&J DOES NOT DISPUTE THE RELIABILITY OF DR. LONGO'S METHODOLOGIES, ONLY THE *APPLICATION* OF METHODOLOGIES THAT J&J CONCEDES ARE RELIABLE

J&J does not contend that any of the scientific methodologies Dr. Longo used are themselves unreliable. J&J objects only to Dr. Longo's ***application*** of these generally accepted testing procedures. Under such circumstances, Dr. Longo's opinions are admissible.

Dr. Longo strictly applied published, generally accepted methodologies to determine whether there were asbestos structures in J&J's talcum powder: (i) preparation through the heavy liquid separation method; and (ii) the TEM three-step test: morphology, EDXA and SAED.[210] J&J suggests no alternative methodologies to test for asbestos in talc. How could it? J&J itself employed the ***same*** methodologies to test for asbestos in its talc.[211]

J&J moves to exclude Dr. Longo's testimony on the basis that Dr. Longo did not properly ***apply*** the otherwise reliable methodologies in reaching his opinion. Third Circuit law does not permit exclusion of an expert's opinion where there is a

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[209] *See* Shukla, et al. (2009) at 114-123; Buz'Zard (2007) at 579-586; Akhtar, et al., (2010) at 1139; and Akhtar, et al. (2012).
[210] Longo Hr'g Tr. at 544:23-545:9; Longo Hr'g Slide, attached as **PD Exhibit 8**.
[211] See *infra* Section V(E).

discrepancy in the application of a reliable methodology, absent a serious misstep that infects the entire opinion. There were no missteps, much less egregious missteps, in Dr. Longo's application of these generally accepted methodologies. Indeed, at the *Daubert* Hearing, J&J did not cross-examine Dr. Longo on his application of most of the methodologies he employed.[212]

A. DR. LONGO IS QUALIFIED

1. Dr. Longo chaired EPA committees charged with formulating a reliable standard for detecting asbestos in diverse materials

J&J does not contend that Dr. Longo is unqualified to test for the presence of asbestos in talc. However, because part of this Court's consideration in evaluating whether a particular scientific methodology is reliable, including the testability of the expert's hypothesis, includes the degree to which the expert testifying is qualified,[213] this Court must also consider that Dr. Longo was charged with formulating the Environmental Protection Agency (the "EPA") testing methodologies for detecting the presence of asbestos in materials.

Dr. Longo has tested for the presence of asbestos in materials for over 35 years.[214] Dr. Longo was selected to serve on the EPA peer review group for their

[212] Dr. Longo has been designated to testify about the presence of asbestos in J&J's TPP. Dr. Longo has not been designated to provide plaintiff-specific testimony. Therefore, for purposes of these MDL proceedings, Dr. Longo will not be providing an opinion about the amount of asbestos or fibrous talc exposure that any of the plaintiffs sustained.
[213] *Paoli II*, 35 F.3d at 742.
[214] Longo Hr'g Tr. at 445:13-15

asbestos screening program, and to provide guidance to the EPA on the proper methodologies for testing samples for asbestos.[215] He was further selected to serve on a second EPA committee to determine the asbestos concentrations per area of building dust.[216] This collaboration with the EPA resulted in the publication of the American Society for Testing of Materials ("ASTM") publication D-5755 for analysis of asbestos in building materials. He chaired the EPA committee that developed the standardized test method for testing materials for asbestos with a transmission electron microscope ("TEM"), resulting in the publication of ASTM D 5755-55. The ASTM 5755 standard was a consensus among multiple scientists, including scientists consulting for J&J, on the best method to test materials for the presence of asbestos by use of transmission electron microscopy.[217]

2. Dr. Longo's laboratory and his analysts are certified to test materials for the presence of asbestos

Dr. Longo's laboratory, MAS, is certified by the National Voluntary Laboratory Accreditation Program, run by the National Institute of Standard and Technology, for the analysis of asbestos in materials.[218] All of his laboratory analysts were required to follow the generally-accepted test methods for TEM and PLM.[219]

[215] *Id.* at 448:9-449:4.
[216] *Id.* at 449:16-450:24
[217] *Id.* at 450:25-451:3; 451:4-453:22; 453:8-454:21
[218] *Id.* at 454:22-455:23.
[219] *Id.* at 649:20-25.

They receive extensive training in the use of TEM and PLM, and have decades of experience. All of his analysts have a Bachelor's Degree in biological science.[220] Anthony Keaton, who performed the TEM analysis on J&J talc, is a geologist and mineralogist. Dr. Longo's manager of PLM and TEM has fifteen years of experience. [221] Dr. Longo assures that the correct protocols are being used, double-checks work, and reviews the images underlying the results.[222] He confirms the reliability of his analysts by their supervision, the quality control, the co-efficient variation for error rates, and continual monitoring.[223]

B. DR. LONGO EMPLOYED A RELIABLE METHODOLOGY

1. Using the heavy liquid concentration method and the TEM three-step method, Dr. Longo found asbestos in 60% of the samples

Using TEM, Dr. Longo detected amphibole asbestos[224] in 42 of the 71 J&J talc samples tested.[225]

[220] *Id.* at 500:20-501:16; 501:17-502:1.
[221] *Id.* at 500:20-502:1; 501:17-502:1; 502:6-16.
[222] *Id.* at 502:6-17.
[223] Longo Hr'g Tr. at 650:1-10.
[224] It is undisputed that once asbestos is a known human carcinogen that can cause cancer of the ovary. IARC (2012) at 219, 253-256, 294.
[225] Longo Hr'g Tr. at 529:12-25; Longo Hr'g Bench Book ("Bn. Bk.") at Tab 28, MAS 2/1/2019 Rep. at 17, ECF No. 10066, Ex. 90. These results are consistent with J3's results detecting asbestos in approximately 60% of J&J samples when it applied the same methodology (i.e. heavy liquid separation followed by TEM). *See* Longo Hr'g Bn. Bk. at Tab 29A; Longo Hr'g Slides at 97; Longo Hr'g Tr. at 628:12-21.

Dr. Longo used the heavy liquid concentration method to "concentrate the potential amphibole asbestos that might be present so that you can remove the interference of all the talc that causes a problem with the analysis," and J&J did not object to the reliability of this methodology, nor to Dr. Longo's application of it.[226] This method was published in Environmental Health Prospectus, part of the National Institute of Environmental Health Sciences, by J&J consultant and Rutgers' Professor of Geology Dr. Alice Blount.[227] The heavy liquid separation method has been used for "years and years and years in the mineral industry to remove different density materials."[228] In 1974, the heavy liquid preparation method was developed by consultants for J&J, including Dartmouth College, to increase the sensitivity of testing for asbestos in talc.[229] In 2014, ISO published the test method of heavy liquid separation for analyzing talc for asbestos, ISO standard 22262-2.[230] Critically, it specifies that an "Optimum Analytical Procedure" for analyzing asbestos in talc is to use the heavy liquid concentration method.[231]

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[226] Longo Hr'g Tr. at 475:17-476:3.
[227] Longo Hr'g Bn. Bk. at Tab 13, ECF No. 10066, Ex. 23; Longo Hr'g Tr. at 476:4-477:10.
[228] *Id.* at 478:22-479:5.
[229] Longo Hr'g Bn. Bk. at Tab 17, attached as **PD Exhibit 9**; Longo Hr'g Tr. at 479:6-480:23, 482:17-21.
[230] Longo Hr'g Tr. at 483:6-485:14, Longo Hr'g Bn. Bk. at Tab 18, ECF No. 10042, Ex. 6.
[231] ISO 22262-2 at 1, 38, Longo Hr'g Bn. Bk. at Tab 18; Longo Hr'g Tr. at 484:25-485:14.

When J&J questioned Dr. Longo as being the "only" expert to test talc for asbestos in the manner in which he did,[232] this difference arises solely from the fact that Dr. Longo applied a heavy liquid separation technique in addition to the three-step TEM published method.[233] Notably, at no point does J&J argue that the heavy liquid separation method is an unreliable methodology, nor did J&J critique Dr. Longo's application of this methodology.

2. Dr. Longo applied the published, peer-reviewed three-step TEM method to determine if there is asbestos in J&J's talc

Per ISO 22262-2, after employing the heavy liquid separation method by means of centrifugation, the next step is to "[i]dentify any ***asbestiform*** amphibole in the centrifuge according to procedures specified in ISO 22262-1" which are PLM, SEM, ***or*** TEM.[234] Dr. Longo first applied the TEM three-step method.

3. The TEM three-step method is recommended by three separate testing standards, *and* J&J

The EPA AHERA, ASTM 5755, ISO 22262-1 and -2, and J&J ***all*** provide for the use of the TEM three-step method to analyze for asbestos in materials, including specifically for talc.[235]

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[232] Longo Hr'g Tr. at 544:23-545:14.
[233] *Id.* at 544:23-545:19; *see also supra* n. 232 (Dr. Alice Blount applied heavy liquid separation prior to testing by PLM).
[234] Longo Hr'g Bn. Bk. at Tab 18, ISO 22262-2, at 8, 29-30 (emphasis added).
[235] Longo Hr'g Tr. at 568:16-18, 648:21-649:11, 666:9-14 (testifying that if the three-step method is met; the particle is asbestos).

- **EPA AHERA**: The EPA Asbestos Hazard Emergency Response Act ("AHERA") method was developed by the EPA through a consensus of leading scientists to develop a test method to ensure the efficacy of abating asbestos from schools.[236] The EPA AHERA was the "unanimous conclusion" of the microscopists with "extensive experience" for the detection of asbestos.[237] The EPA AHERA method eliminates all non-asbestos particles by means of the TEM three-step method: "Nonasbestos" is defined as "Incomplete or unobtainable ED patterns [**Step #3**], a nonasbestos EDXA [**Step #2**], or a nonasbestos morphology [**Step #1**]."[238]

- **ISO 22262-1 and 22262-2**: The International Organization for Standardization ("ISO") is a worldwide federation of national standards bodies.[239] ISO Method 22262-1 and -2 specify the procedures for the quantitative analysis of asbestos in talc.[240] ISO 22261-1 and -2 expressly provide for the use of the TEM three-step method for testing for the presence of asbestos in talc.[241] Additionally, ISO 22262-2 provides that for testing for the presence of asbestos in talc, the "optimum method" is to first concentrate the amphiboles by means of heavy liquid separation, and then apply the TEM or PLM.[242]

- **ASTM 5755**: American Society for Testing Materials ("ASTM") Standard ASTM D 5755-55 was developed by an EPA committee of multiple scientists, which Dr. Longo chaired. [243] ASTM 5755 requires use of the TEM three-step method.[244]

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[236] *Id.* at 493:12-494:10.
[237] Longo Hr'g Bn. Bk. at Tab 20, 52 Fed. Reg. 41826, 41839 (Oct. 30, 1987), attached as **PD Exhibit 10**; Longo Hr'g Tr. at 494:6-495:4.
[238] *Id.* at Tab 21, EPA AHERA at 893, ECF No. 10042, Ex. 5.
[239] *Id.* at Tab 18, ISO 22262-2 at v.
[240] *Id.* at Tab 25, ISO 22262-1 at 1, ECF No. 10066, Ex. 97.
[241] Longo Hr'g Tr. at 483:13-23, 495:17-495:5, 508:14-509:17, 511:8-512:20, 594:14-16, 652:2-11.
[242] Longo Hr'g Bn. Bk. at Tab 18, p. 38.
[243] Longo Hr'g Tr. at 451:4-453:22; Longo Hr'g Bn. Bk. at Tab 19, attached as **PD Exhibit 11**.
[244] *See id.* at Tab 19, ASTM D5755-09 at 1.

- **J&J**: J&J employed the TEM three-step method for testing talc for asbestos.[245]

J&J criticizes Dr. Longo for failing to employ a methodology employed by the government to test for asbestos in talc. But the FDA has never adopted a test method for talc.[246] Nor has the government adopted a method for testing asbestos in talc.[247] J&J questioned Dr. Longo as to why he did not use the USP method.[248] But the USP expert panel is critical of the current procedures used by the USP talc method, because this method suffers from multiple deficiencies, including its use of infrared analysis and X-ray diffraction.[249] No government agency, including the EPA and OSHA, uses infrared analysis to determine asbestos in bulk samples. As for x-ray diffraction, it has, as the USP expert panel concurs, a relatively high detection limit for asbestos, allowing large amounts of asbestos to pass undetected.[250]

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[245] *See id.* at Tab 6, JNJNL61_000043150-43151, attached as **PD Exhibit 12**.
[246] Longo Hr'g Tr. at 651:3-9.
[247] *Id.* at 651:17-20.
[248] *Id.* at 546:11-25.
[249] *Id.* at 637:13-640:33; Longo Hr'g Ex. 4, Block, et al., *Stimuli to the revision process: Stimuli articles do not necessarily reflect the policies of the USPC or the USP Council of Experts*, attached as **PD Exhibit 13** (available at http://www.usppf.com/pf/pub/data/v404/GEN_STIMULI_404_s201184.html).
[250] Longo Hr'g Tr. at 638:15-20; 638:21-640:4.

4. Dr. Longo has published on the use of the TEM three-step method in the peer-reviewed literature

Dr. Longo has published in the peer-reviewed literature on the use of the three-step TEM method to determine the presence of asbestos in multiple diverse substances.[251] Notably, these tests were used to detect asbestos in materials where it would otherwise not be suspected, such as cigarette filters, lung tissue, and vermiculite,[252] defeating J&J's unsupported theory that Dr. Longo applied a test that is only used on products that are known to contain asbestos.[253]

[251] Longo Hr'g Bn. Bk. at Tabs 10 (attached as **PD Exhibit 14)**, 11 (Longo, et al., *Fiber release during the removal of asbestos-containing gaskets: a work practice simulation*, 17 Applied Occupational and Environmental Hygiene 55-62 (2002), attached as **PD Exhibit 15**), and 12 (attached as **PD Exhibit 16**); Longo Hr'g Tr. at 474:15-5, 488:5-489:16.

[252] *See*, William Longo et al., *Crocidolite Asbestos Fibers in Smoke from Original Kent Cigarettes*, 55 Cancer Research 2232, (June 1, 1995) (asbestos in cigarette filters) [Longo Hr'g Tr. at 489:5:-23; Longo Hr'g Bn. Bk. at Tab 10]; William Longo and Victor Roggli, *Mineral Fiber Content of Lung Tissue in Patients with Environmental Exposures: Household Contacts vs. Building Occupants*, The Third Wave of Asbestos Disease: Exposure to Asbestos in Place, Annals of The New York Academy of Sciences, Vol. 643 (asbestos in lung tissue) [Longo Hr'g Tr. at 490:4-491:17; Longo Hr'g Bn. Bk. at Tab 10A, attached as **PD Exhibit 17**]; Ewing et al., *Zonolite Attic Insulation Exposure Studies*, 16 Int. J. Occup. Environ. Health 279 (2010) (use of the TEM three-step method to identify tremolite and actinolite asbestos in Libby, Montana vermiculite) [Longo Hr'g Tr. at 491:18-493:4, 585:6-25; Longo Hr'g Bn. Bk. at Tab 12].

[253] ECF No. 9736-3 at 33 (arguing that Dr. Longo uses a methodology "developed for identifying the amount of asbestos known to be present").

C. DR. LONGO STRICTLY APPLIED THE TEM THREE-STEP TESTING METHOD

1. Step One: Morphology

Applying the EPA AHERA methodology to confirm that the morphology correlates with that of an asbestos fiber, Dr. Longo analyzed whether the structures he found in the J&J talc had an aspect ratio greater than or equal to 5:1 and a length greater than or equal to 0.5 micrometers.[254] These are the same counting rules as promulgated by ASTM and ISO.[255] The EPA adopted the 5:1 aspect ratio, because "[i]t is consistent with the panel of microscopists' observations that asbestos structures have aspect ratios equal to and greater than 5:1 whereas the majority of nonasbestos structures, minerals and particles, for example, gypsum, have aspect ratios of less than 5:1."[256]

[254] Longo Hr'g Tr. at 495:5-9; Longo Hr'g Bn. Bk. at Tab 21, 40 CFR Ch. 1, App'x A to Subpart E of § 763 at 871.

[255] Longo Hr'g Tr. at 495:5-14; 497:11-19; *see also* Longo Hr'g Bn. Bk. at Tab 22, James Millette, *Procedure for the Analysis of Talc for Asbestos*, 61 The Microscope 1, at 16 (2015) ("Comparison of the aspect ratio plots in the 1977 Bureau of Mines Circular (26) shows that a criterion of about 5:1 aspect ratio appears to be the best aspect ratio discriminator for asbestos versus non-asbestos fibers. The 5:1 aspect ratio is used in AHERA; ASTM methods D6281, D5755, D5756 and D6480; and ISO 10312 and 13794."), attached as **PD Exhibit 18**.

[256] Longo Hr'g Bn. Bk. at Tab 20, at 41840.

2. Step Two: EDXA

The next step of Dr. Longo's peer-reviewed, published three step method is the Energy Dispersive X-ray Analysis ("EDXA").[257] This allows an analyst to determine the chemistry of the fiber being examined.[258] The point of the EDXA analysis is to "compare spectrum profiles with profiles obtained from asbestos standards."[259] "The closest match identifies and categorizes the structure."[260]

Again, J&J does not claim that EDXA is an unreliable methodology; J&J criticizes Dr. Longo's ***application*** of this methodology because Dr. Longo did not provide the numerical results for the chemical elements.[261] But no methodology requires the production of the numerical elements.

First, the EPA AHERA method does not require that the numerical value of each element is reproduced below the EDXA spectrum.[262] On the contrary, the EPA AHERA method requires a "semiquantitative comparison" with the reference spectra.[263] ***Second***, J&J's expert Dr. Dyar conceded that she could not cite any standard requiring EDXA data formulation printouts.[264] ***Third***, Dr. Longo's

[257] Longo Hr'g Tr. at 502:23-503:4; *see, e.g.*, Longo-MDL_00324, Longo Hr'g Bn. Bk. at Tab 9C, attached as **PD Exhibit 19**.
[258] Longo Hr'g Tr. at 502:23-503:4.
[259] Longo Hr'g Bn. Bk. at Tab 21, 52 CFR 41846, Subpt. E, App. A at 871.
[260] *Id.* at Tab 21, EPA AHERA at 893.
[261] ECF No. 9736-3 at 64-66.
[262] Longo Hr'g Tr. at 504:1-7.
[263] *Id.* at 504:13-505:6.
[264] Dyar Depo. at 124:14-131:17, 137:2-129:9.

laboratory followed the precise specifications of ASTM D5755, which requires the analyst to "record at least one X-ray spectrum for each type of asbestos observed per sample. Attach the print-outs to the back of the count sheet."[265] The quantitative results for the chemical composition of the fibers are not required under ASTM D5755.[266] ***Fourth***, ISO 22262-1, the method for testing talc for asbestos, does not require the analyst produce the quantitative results for the fibers' chemical composition; the analyst looks to see if the "peaks" are "comparable in ratio" to the referenced exemplars.[267] "It is a visual comparison to the standard."[268] Notably, despite extensive briefing criticizing Dr. Longo's lack of quantification in using EDXA, J&J had ***no questions*** for Dr. Longo at the *Daubert* Hearing on this matter after Dr. Longo explained that such quantification is not required.

3. Step Three: SAED

The EPA AHERA requires a "visual identification of electron diffraction (ED) patterns" to confirm that a fiber is asbestos.[269] SAED shows a pattern of dots

[265] Longo Hr'g Tr. at 505:7-23; Longo Hr'g Bn. Bk. at Tab 9A, Longo-MDL_00878, attached as **PD Exhibit 20**.
[266] Longo Hr'g Tr. at 505:24-506:7.
[267] Longo Hr'g Bn. Bk. at Tab 25, ISO 22262-1 at 34; Longo Hr'g Tr. at 506:8-11.
[268] *Id.* at 506:16-24.
[269] Longo Hr'g Bn. Bk. at Tab 21, EPA AHERA at 873-874, 893 (detailing patterns for chrysotile asbestos and amphibole asbestos); Longo Hr'g Tr. at 507:3-15.

that reflect the arrangement of atoms of the minerals, revealing its crystal structure and accordingly its mineral type.[270]

This third step enables the analyst to distinguish between fibrous talc and anthophyllite asbestos, by tilting the fiber along the goniometer, which Dr. Longo did here.[271] Again, J&J does not object that SAED is an unreliable methodology; J&J objects only to Dr. Longo's ***application*** of the methodology. J&J argues that Dr. Longo misapplied the SAED analysis by not conducting a dual zone-axis measurement.[272] But, the EPA AHERA method does not require a dual zone axis measurement.[273] On the contrary, the EPA AHERA method requires the analyst to "[v]erify the identification of the pattern by measurement or comparison of the pattern with patterns collected from standards under the same conditions."[274] MAS followed this protocol.[275] ISO 22262-1 also does not require dual zone axis;[276] it states "[a]nalysis of laboratory samples seldom requires zone-axis measurements."[277] Additionally, Dr. Longo followed the ASTM 5755 protocol for SAED, which does not require dual zone-axis measurements.[278] Finally, J&J's own

[270] Longo-MDL_00325 (Tremolite Diffraction at 50cm), attached as **PD Exhibit 21**.
[271] Longo Hr'g Tr. at 508:14-509:17.
[272] ECF No. 9738-3 at 53-57.
[273] Longo Hr'g Tr. at 507:16-508:4.
[274] Longo Hr'g Bn. Bk. at Tab 21, EPA AHERA, p. 899.
[275] Longo Hr'g Tr. at 508:5-13.
[276] *Id.* at 509:10-17.
[277] Longo Hr'g Bn. Bk. at Tab 25, ISO 22262-1 at 64.
[278] Longo Hr'g Tr. at 510:23-511:7.

protocols for measurement by SAED do not require zone-axis measurements.[279] Notably, despite extensive briefing contending that a dual zone axis measurement is required, J&J had ***no questions*** for Dr. Longo at the *Daubert* hearing on this matter after Dr. Longo explained that no methodology requires a dual zone axis measurement.

D. REPRODUCIBILITY: DR. LONGO'S TEM RESULTS WERE REPRODUCED WITH A MINIMAL ERROR RATE

MAS measured the error rate of four TEM analysts counting asbestos structures, and the co-efficient of variation showed an error rate of only +/- 6%.[280]

Using TEM, a separate laboratory, J3 Resources, analyzed 22 asbestos structures that Dr. Longo's laboratory reported as asbestos, and verified that they were all either tremolite or anthophyllite structures, and 20 out of 22 were asbestos, yielding an over 90% validation rate.[281] Additionally, using the same methodology of heavy liquid separation plus the TEM three-step method, J3 detected asbestos in approximately 68% of J&J talc samples.[282]

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[279] *Id.* at 513:12-514:3; *see also* Longo Hr'g Bn. Bk. at Tab 6, JNJNL61_000043153, *and id.* at Tab 6A, JNJNL61_000005038, attached as **PD Exhibit 22**.
[280] Longo Hr'g Tr. at 524:21-525:16; Longo Hr'g Bn. Bk. at Tab 52, MAS Coefficient of Variation Report (9/6/18), attached as **PD Exhibit 23**.
[281] Longo Hr'g Tr. at 527:1-528:11; Longo Hr'g Bn. Bk. at Tab 29, J3 Resources 11/7/18 Report at 1-2, attached as **PD Exhibit 24**.
[282] *Id.* at Tab 29A, attached as **PD Exhibit 25**; Longo Hr'g Tr. at 628:12-21.

E. CORROBORATION WITH GEOGRAPHIC TALC FORMATIONS

Dr. Longo's findings were corroborated by the reports of Drs. Krekeler and Cook: "They identified the same type of asbestos that we are seeing in the Italy mine, the Vermont mine, and compared that also to Johnson & Johnson's own test for those particular mines for cosmetic talc. We are consistent with they say that is in there because of the geological formation as well as the literature as well as the testing done by Johnson & Johnson."[283]

F. DR. LONGO ALSO PERFORMED AN ANALYSIS BY PLM, WHICH WAS CONSISTENT WITH HIS FINDINGS BY TEM

Dr. Longo also verified the presence of asbestos in J&J talc samples by means of polarized light microscopy ("PLM"), strictly following the standards set forth in ISO 22262-1 to identify for the presence of asbestos: morphology, colour and pleochroism; birefringence; extinction characteristics; sign of elongation; and refractive indices.[284]

ISO 22262-1 confirms that using this method of morphology by PLM, the analyst confirms the "asbestiform habit."[285] Dr. Longo found asbestos in over 60%

[283] *Id.* at 539:1-10.
[284] Longo Hr'g Bn. Bk. at Tab 25, ISO 222262-1 at 21.
[285] *Id.* at 22-23.

of the samples when he used heavy liquid separation followed by PLM which is consistent with his findings for TEM.[286]

J&J does not contend that PLM by means of ISO 22262-1 was an unreliable methodology to detect for the presence of asbestos fibers in talc. J&J's complaint was in the ***application***, in that J3 was unable to reproduce the MAS results when applying PLM without first using the heavy liquid concentration method.[287]

G. THERE WERE NO FLAWS IN DR. LONGO'S APPLICATION OF THE RELIABLE METHODOLOGIES, LET ALONE MAJOR FLAWS WARRANTING EXCLUSION

1. J&J's objections to the application of the TEM three-step process and PLM do not warrant exclusion

J&J does not dispute that heavy liquid separation, the TEM three-step process, or PLM used with heavy liquid separation are reliable methodologies. Thus, the evidence before this Court is that Dr. Longo used methods that have been tested and subjected to peer review and publication, that are governed by controlling standards, and that enjoy acceptance within the scientific community. J&J's criticisms as to the

[286] *Id.* at Tab 9, MAS 1/15/19 Report at 16, attached as **PD Exhibit 26**; *see also* Longo Hr'g Tr. at 530:18-537:16; Longo Hr'g, Exhs. 3A-3J (pictures of PLM optical micrographs), attached as **PD Exhibit 27**.
[287] ECF No. 9736-3 at 76.

application of these reliable methodologies have no merit, and certainly are not sufficient to warrant exclusion.[288]

Heavy Liquid Separation: J&J does not object to Dr. Longo's use of the heavy liquid separation method, nor to his application of this method.

TEM Three-Part Test: J&J's objections to the application of the TEM three-part test are without merit. ***First***, for determination of morphology ("counting"), J&J erroneously argues that Dr. Longo only used the counting criteria to determine if a fiber is asbestos, and thus it was "overinclusive."[289] On the contrary, Dr. Longo testified that he first eliminated non-asbestos fibers that did not meet the requisite morphological criteria, but then subjected the fibers to a further analysis by SAED and EDXA to confirm they are asbestos. ***Second***, as set forth *supra* at Section V(C)(2), no procedure requires an analyst to provide numerical chemical numbers below the graph, as J&J's expert Dr. Dyer concedes. ***Third***, SAED does not require a dual zone axis measurement.[290] J&J cites to *Hanson v. Colgate-Palmolive Company*, 363 F.Supp.3d 1273, 1281 (2018), for the principle that SAED requires two different zone-axis measurements under the Yamate Level III method, a 1984 methodology. But, the EPA did not adopt the Yamate Level III method in

[288] *See, e.g. Paoli II*, 35 F.3d at 767 (district court erred in excluding medical opinion, even though the experts conclusion may have been incorrect, where the methodology followed was "reasonably reliable.").
[289] ECF No. 9736-3 at 34.
[290] *See supra* at Section V(G)(3).

promulgating its AHERA standard.[291] Nor does the *Hanson* trial court reconcile outdated Yamate with the more recent published standards in AHERA, ISO 22262-1, and ASTM 5755; indeed, it appears that these methodologies were not brought to the trial court's consideration. Moreover, in direct contradiction to *Hanson*, recently a trial court concluded that, under a *Daubert* standard, the absence of a dual zone axis measurement did ***not*** affect the reliability of the expert's testing method: "[T]he Court is not persuaded that [the expert's] opinions are unreliable because he did not utilize the dual zone axis method in his analysis, as the testimony established such a methodology is in fact ***not*** in regular use in the scientific community."[292]

PLM: J&J disputes Dr. Longo's ***application*** of PLM because the J3 laboratory was not able to replicate Dr. Longo's results when using PLM without the concentration method. Critically, the J3 Lab did its PLM without first doing heavy liquid separation. This made the PLM method not as sensitive.[293] Similarly, when MAS performed the PLM without heavy liquid separation, it found asbestos in only 30% of the samples, as opposed to 60% when using heavy liquid separation.[294] ISO 22262-2 specifically states that it is not an "optimum procedure"

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[291] Longo Hr'g Tr. at 494:15-495:4.
[292] *Hayes v. Colgate-Palmolive*, No. 16-CI-004503, Jefferson Circuit Court, Div. 10, Kentucky (7/12/2019) at 4 (original emphasis), Longo Hr'g Bn. Bk. at Tab 29B, attached as **PD Exhibit 28**.
[293] Longo Hr'g Tr. at 632:13-633:19.
[294] *Id.* at 537:6-16 ("So the heavy liquid separation was more sensitive. It almost doubled the positives."), 633:20-25.

to use PLM without first doing heavy liquid separation.[295] The results of both Dr. Longo and J3 confirm that analysis of talc by PLM, ***without first doing heavy separation***, is a less sensitive analysis for detecting asbestos in talc, which is why this method is not specified as an "optimum procedure" by ISO.

In contrast, when Dr. Longo ***did*** use the "optimum technique" in his PLM analysis, first applying the heavy liquid concentration method, he found 60% of the samples contained asbestos, which is entirely consistent with his results when he tested the pre-concentrated talc by TEM, and consistent as well with J3 detecting asbestos in approximately 60% of J&J talc samples when it applied the same methodology (i.e. heavy liquid separation followed by TEM).[296]

2. J&J's remaining criticisms: all go to the weight, not the admissibility of the evidence

a. No methodology requires the analyst to ascertain the manner in which the fibers were formed to classify them as asbestos

J&J argues that Dr. Longo did not divine the manner in which the fibers were formed, such that Dr. Longo could say that the fibers are "asbestiform."[297] But J&J appears to willfully ignore that the methodologies employed by Dr. Longo provide that if a fiber meets the requisite criteria, it is asbestos. The EPA stated that "It is the

[295] *Id.* at 635:4-7; Longo Hr'g Bn. Bk. at Tab 18, ISO 22262-2 at 38.
[296] *Id.* at Tab 29A; Longo Hr'g Slides at 97; Longo Hr'g Tr. at 628:12-21.
[297] ECF No. 9736-3 at 5-6.

position of EPA, the U.S. Centers for Disease Control and Prevention, Agency for Toxic Substances and Disease, Registry and National Institute for Occupational Safety and Health, and the American Thoracic Society, among others, that microscopic structures of amphibole and serpentine materials that are asbestiform and meet the size definition of PCM fibers should be counted as asbestos regardless of the manner in which they were formed."[298] Dr. Longo testified that he strictly adhered to ISO22262-1 protocol for analysis to determine if there is amphibole asbestos in J&J talc.[299] The ISO standard explicitly provides that using this method enables the analysis to determine whether the fibers are "asbestiform."[300]

b. <u>The fiber versus bundle argument is a strawman</u>

J&J attempts to create a strawman by arguing that "Drs. Longo and Rigler's identification of 'bundles' is fundamental to their visual TEM analysis," and because there were conflicts in the analysts classification of fiber versus bundle, Dr. Longo cannot reliably conclude that a fiber is asbestos.[301] But nowhere does the TEM three-step method require a distinction between fibers versus bundles to determine whether a fiber is "asbestiform."[302]

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[298] Longo Hr'g Tr. at 661:18-662:25, 647:1-12; Longo Hr'g Bn. Bk. at Tab 43, Ex. 1, attached as **PD Exhibit 29**.
[299] Longo Hr'g Tr. at 530:18-533:9; 531:18-532:15.
[300] Longo Hr'g Bn. Bk. at Tab 25, ISO 22262-1 at 22-23.
[301] ECF No. 9736-3 at 40.
[302] *See supra* Section V(G).

First, the generally accepted TEM three-step method is capable of classifying a single fiber as asbestos.[303] Under the published TEM methods, both fibers and bundles are asbestos.[304] ***Second***, the "test" that J&J criticizes was not designed to discern between fibers and bundles. Dr. Longo explained that "[t]his test was only designed to determine the counting statistics. We never asked the analysts to do a fiber bundle agreement study."[305] ***Third***, there was 72.2% agreement as to whether tremolite structures were fibers or bundles.[306] For anthophyllite, there was 83.7% agreement. ***Finally***, Dr. Longo testified that every year his laboratory is subject to a NVLAP audit testing on the issues of fibers and bundles, and for the 2017 testing performed by NVLAP, the level of consistency in terms of validation of the analysts that tested J&J's talc for asbestos to accurately determine whether the asbestos structure is a fiber or a bundle was above 95 percent agreement.[307] For the previous three years, 2016, 2015, and 2014, they were all above 95 percent agreement.[308]

In sum, J&J's only complaints as to Dr. Longo's testing for the presence of asbestos in its talc apply to the ***application*** of what J&J concedes are reliable

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[303] Longo Hr'g Tr. at 520:1-23; Longo Hr'g Bn. Bk. at Tab 18, ISO 22262-2 at 7 ("The limit of quantification using this part of ISO 22262 is defined as the detection and identification of one fibre or fibre bundle.").
[304] Longo Hr'g Tr. at 524:1-20; Longo Hr'g Bn. Bk. at Tab 21, EPA AHERA at 871; *id*. at Tab 19, ASTM D5755-09 at 2, 8.
[305] Longo Hr'g Tr. at 603:16-24
[306] *Id.* at 524:21-526:19.
[307] *Id.* at 526:20-25; 668:3-25.
[308] *Id.*

methodologies.[309] None of J&J's alleged "errors" in application (which Plaintiffs dispute in the first instance) so altered the underlying the methodology so as to skew the methodology itself.[310] For TEM, Dr. Longo properly determined by morphology, chemistry, and crystal composition that certain fibers were asbestos. For PLM, he strictly applied the ISO 22262-1 standard, which J&J does not dispute.

J&J's objections to Dr. Longo's ***application*** of methods that J&J's concedes are reliable do not warrant exclusion under Third Circuit law. Properly applying *Daubert*, these are matters for the jury to consider in analyzing the weight to be given Dr. Longo's testimony.

VI. THE CONSTITUENTS OF TALCUM POWDER PRODUCTS PROVIDE ADDITIONAL EVIDENCE IN SUPPORT OF A BIOLOGICALLY PLAUSBILE MECHANISM

The PSC's experts properly considered all ingredients in the TPP (including asbestos as discussed above). The presence of these constituents help explain why the epidemiological studies establish that women who use TPP are at a heightened risk for developing ovarian cancer. The devil is in the details—like cigarettes, TPP contains a dangerous combination of human carcinogens that contribute to its carcinogenic properties.

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[309] "An alleged error in the application of a reliable methodology should provide the basis for exclusion of that opinion only if the error negates the basis for the reliability of the principle itself." *United States v. Martinez*, 3 F.3d 1191, 1198 (8th Cir. 1993).
[310] *Id.* (*citing In re Paoli R.R. Yard PCB Litig.*, 916 F. 2d 829, 858 (3d Cir. 1990)).

A. FIBROUS TALC AND THE HEAVY METALS NICKEL, CHROMIUM, AND COBALT

Evidence establishes beyond dispute that fibrous talc, nickel, chromium, and cobalt: (1) are present in TPP and have been for decades; (2) reach and become enmeshed in the ovaries when applied to the genital area; and (3) contribute to the development of cancer through a well-understood and accepted biological mechanism—inflammation. The PSC's experts' methodology in evaluating and considering the presence of these constituents of TPP was reliable.

1. Fibrous talc and the heavy metals nickel, chromium, and cobalt are present in J&J's TPP

Talc is a mineral, and like other minerals, it can occur in a fibrous form often referred to as an "asbestiform habit." Fibrous talc is present in TPP and has been for decades. J&J and Imerys produced tests spanning from 1945-1999 that show the Italian and Vermont mines used to source TPP contained fibrous talc.[311] J&J's own analyses show that fibrous talc occurred in up to 10% of the talc ore from the Hammondsville Mine in Vermont.[312] The testing performed by the PSC's experts Drs. Longo and Rigler on bottles of TPP corroborated J&J's internal documents and testing—fibrous talc was present in 98% of the bottles tested.[313] Nickel, chromium,

[311] Krekeler Rep. at 23-29, ECF No. 9885, Ex. 12

[312] *See* JNJS7IR_000001978-2124, Colorado School of Mines testing at Hammondsville mine in Vermont, ECF No. 9885, Ex. 64.

[313] *See* Longo Rep. at 9, 21, ECF No. 10066, Ex. 90 ("The MAS ISO 2226201 PLM analysis showed that fibrous talc was found in 56 of 57 total samples").

and cobalt are also present in TPP. Here again, J&J's own internal documents conclusively establish that the heavy metals were present in the mines used to source TPP and in the resulting finished product.[314] It is beyond dispute that women who habitually apply TPP to their perineum are exposing themselves to fibrous talc, nickel, chromium, and cobalt.

2. Fibrous talc and the heavy metals nickel, chromium, and cobalt can and do become embedded in ovarian tissue when applied to the perineal area

Once TPP reaches the ovaries, it sequesters in the ovarian tissue. Ovulation causes an open wound on the surface of the ovary.[315] When platy talc, fibrous talc, heavy metals, etc. are present near the ovary at that time, they can be incorporated into the healing sore and lodge in the ovarian tissue. And, when the particulates become enmeshed or sequestered in the ovarian tissue, there is no natural mechanism by which they can be eliminated. Unlike human lungs, which have a "well-designed system" for purging foreign particles, the ovaries have no such elimination system.[316] J&J has wholly failed to show otherwise, despite repeatedly criticizing Dr. Carson's use of the phrase "no intrinsic elimination system" at his deposition and the *Daubert* Hearing.

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[314] *See*, *e.g.*, ECF No. 9885, Exs. 6, 7, and 8.
[315] Clarke-Pearson Hr'g Tr. at 1550:12-1551:17.
[316] Carson Hr'g Tr. at 1283:8-1284:18 (citing Cramer et al., (2007)); Clarke-Pearson Hr'g Tr. at 1554:14-25; 1285:1-19.

3. Fibrous talc and the heavy metals nickel and chromium (VI) are IARC Group 1 human carcinogens, and cobalt is currently classified as an IARC Group 2 possible human carcinogen

Once TPP constituents lodge in a woman's ovarian tissue, they can initiate and promote cancer. It is an established scientific fact that fibrous talc, nickel, and chromium are human carcinogens. Fibrous talc is classified by IARC as a Group 1 human carcinogen.[317] Likewise, nickel and chromium (VI) are IARC Group 1 carcinogens. Nickel, chromium (VI), chromium (III), and cobalt are all inflammatory agents, and cobalt is an IARC Group 2 possible human carcinogen.[318]

J&J repeatedly emphasized in its briefing and at the *Daubert* Hearing that there are no studies specifically linking fibrous talc, nickel, chromium, or cobalt to ovarian cancer. But, as Dr. Carson explained, it is not necessary to have studies specifically linking fibrous talc or heavy metals to ovarian cancer because "cancer causation is a fairly general process," and if an agent is carcinogenic to one tissue "we can assume those same mechanisms that lead to carcinogenesis can operate in the ovaries if the potential for exposure exists."[319] IARC's "sufficient evidence" of carcinogenicity standard for a Group 1 classification is met when "a causal

[317] Carson Hr'g Tr. at 1272:25-1273:7; *see* IARC (2012), ECF No. 9885, Ex. 2, 3, 4 (relevant excerpts), ECF No. 9892, Ex. 7 (relevant excerpts).
[318] *See* IARC Monographs on the Evaluation of Carcinogenic Risks in Humans: Volume 86, Cobalt in Hard Metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide (2006) ("IARC 2006"), relevant portion, ECF No. 9885, Ex. 5.
[319] Carson Hr'g Tr. at 1308:14-1309:16.

relationship has been established between exposure to the agent and human cancer" – ***the assessment is not based on the availability of studies on a specific type of cancer***.[320] While specific organs and tissues are certainly identified by IARC where studies have specifically shown an increased cancer risk, the overall assessment focuses on carcinogenicity where the agent operates via a mechanism (like inflammation) that can act on all human organs, including, but not limited to, the epithelial tissue of the ovaries, fallopian tubes, and peritoneal cavity.

During Dr. Carson's testimony, J&J created confusion on the issue of whether IARC classifies fibrous talc as a Group 1 carcinogen by citing to language in what was apparently a non-final and unpublished version of the 2012 IARC monograph.[321] The language cited by J&J described fibrous talc as a cause of lung cancer and mesothelioma, without making specific reference to ovarian cancer.[322] ***This language is not contained in the final, published version of the 2012 monograph***. IARC has confirmed that the version used by the PSC in this litigation is the final, official version because IARC only releases the final version to the public.[323]

[320] IARC (2012), "Preamble" at 21, 22, and 29.
[321] Carson Hr'g Tr. at 1357:2-1358:18 (citing J&J Hearing Exhibit A70 at 309).
[322] *Id.* at 1358:1-4.
[323] *See* August 28, 2019 email from IARC Publications, attached as **PD Exhibit 30**.

J&J's bold and misleading attempt to challenge fibrous talc's carcinogenicity with an ***unpublished version*** of an IARC monograph is unavailing. In 1987, IARC evaluated the carcinogenicity of talc and concluded that there was sufficient evidence that talc containing asbestiform fibers was carcinogenic to humans.[324] To clarify the terminology, in 2010 IARC stated that "[t]he term 'asbestiform fibre' has been mistaken as a synonym for 'asbestos fibre' when it should be understood to mean ***any mineral, including talc***, when it grows in an asbestiform habit."[325] In 2010, IARC also clarified that talc containing asbestos or ***talc containing other asbestiform fibres*** (like talc in an asbestiform habit, i.e. fibrous talc) are Group 1 human carcinogens.[326] And the 2012 IARC monograph explicitly stated that "the conclusions reached [i.e., that they cause cancer in the ovary]…about asbestos and its carcinogenic risks apply to these six types of fibres [chrysotile, actinolite, amosite, anthophyllite, crocidolite, and tremolite] wherever they are found, and ***that includes talc containing asbestiform fibres***."[327] The 2012 Monograph specifically defined "talc containing asbestiform fibres" to include talc fibers.[328] Fibrous talc is

[324] IARC Monograph on Silica and Some Silicates (1987) ("IARC 1987"), ECF No. 9885, Ex. 61 (relevant excerpts); IARC Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, Supplement (1987), ECF No. 9885, Ex. 62 (relevant excerpts).
[325] IARC (2010) at 39 (emphasis added), ECF No. 9885, Ex. 63 (relevant excerpts).
[326] *Id.* at 39.
[327] IARC (2012) at 219, 294 (emphasis added).
[328] *Id.* at 230.

included in the IARC 2012 Monograph because of the well-known carcinogenic properties of mineral fibers that behave in a similar fashion to asbestos regardless of their chemical composition. Fibers cause cancer through a mechanism of inflammation, oxidative stress, cell proliferation, direct and indirect DNA damage, and genetic mutations.[329]

4. Fibrous talc and heavy metals cause inflammation, and inflammation's ability to initiate and promote cancer, <u>including epithelial ovarian cancer, is well-established</u>

Carcinogens generally cause cancer via a two-step process: (1) initiation - a carcinogen initiates the process of carcinogenicity by causing a genetic change or mutation to an existing cell, and (2) promotion - the mutated cell grows and multiplies until it becomes a recognizable tumor. A complete carcinogen is one that participates in both the initiation and promotion of carcinogenesis.[330] Inflammation is a "fundamentally accepted aspect of cancer biology" and a well-established biologic mechanism of cancer.[331] Dr. Carson and Dr. Clarke-Pearson discussed studies at the hearing that recognize the causal connection between chronic inflammation and epithelial ovarian cancer.[332]

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[329] *Id.*; Mossman, Brooke T., *Mechanistic in Vitro Studies: What They Have Told Us About Carcinogenic Properties of Elongated Mineral Particles (EMPs)*, 361 Tox. & Applied Pharmac. 62-67 (2018), ECF No. 9914, Ex. 116.
[330] Carson Hr'g Tr. at 1286:6-17; 1287:2-4.
[331] *See* Levy Dep. at 116:17-24, 117:1-2, ECF No. 9885, Ex. 32.
[332] Carson Hr'g Tr. at 1303:8-1304:3 (citing Ness and Cottreau, *Possible Role of Ovarian Epithelial Inflammation in Ovarian Cancer*, 91 J. Nat'l Cancer Inst. 1459,

Chronic inflammation is the biologic mechanism by which TPP cause ovarian cancer—as Dr. Carson testified, he agrees "with essentially every investigator who's ever looked at this question that talcum powder is a very strong inflammatory agent."[333] Dr. Carson identified and discussed several separate *in vitro* or "cell" studies that uniformly concluded that TPP causes inflammation.[334]

It is likewise well established (and undisputed by J&J) that nickel, chromium, and cobalt cause chronic inflammation,[335] and that the inflammatory properties of nickel and chromium are part of the reason IARC classified them as Group 1 carcinogens.[336] The presence of fibrous talc, nickel, chromium, and cobalt in TPP intensifies the inflammatory response and stimulates cell growth and proliferation (that is, they cause/contribute to the initiation and promotion of cancer).[337] Dr. Carson referred to this phenomenon as "potency" – the addition of carcinogenic components amplifies the overall carcinogenic effect of the talcum powder products

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1463 (1999), ECF No. 9914, Ex. 106; Reuter et al., (2011); and Balkwill and Mantovani, *Inflammation and cancer: back to Virchow?*, 357 Lancet 539, 539 (2001), ECF No. 9914, Ex. 98); Clarke-Pearson Hr'g Tr. at 1567:2-1570:20 (discussing Balkwill and Shan and Lui).

[333] Carson Hr'g Tr. at 1288:2-4.

[334] *Id.* at 1287:17-1290:16 (identifying numerous studies previously provided to the Court); *see also id.* at 1302:9-1303:7 (explaining that talc's inflammatory properties are well understood based on pleurodesis and the ban of talc on surgical gloves).

[335] *Id.* at 1273:17-25 (metals are "primarily catalytic substances that create electrochemical reactions leading to the generation of reactive oxygen species and cellular damage due to disruption of macromolecules, including DNA").

[336] *Id.* at 1309:20-1310:3.

[337] *Id.* at 1293:19-22 (citing Carson Rep. at 7).

as a whole: "[I]f you add carcinogenic materials to something that's already an irritant or even a carcinogen, it will just be more carcinogenic than it was before."[338] Dr. Carson used a demonstrative to explain that fibrous talc and the heavy metals contribute in relative proportions to the carcinogenic power of TPP as a whole.[339]

Contrary to J&J's assertions, it is not true that exposure to the fibrous talc and heavy metals "would be far greater in concentration" in the rectal, vulvar, and vaginal areas, and therefore cause greater inflammation in those areas.[340] As discussed above, the ovaries do not have an intrinsic mechanism for removing foreign particles: "[O]nce it's in, it doesn't get out. It causes chronic inflammation over time."[341] This explains why exposure to TPP and its carcinogenic constituents, causes chronic inflammation in the ovaries but does not cause chronic inflammation or increase a woman's risk of developing cancer in other parts of the reproductive system. Other parts of the reproductive system are "continually washed clean by body fluids that flow over them," and both bathing and menstruation reduce exposure time to the vagina, vulva, rectum, cervix, and uterus.[342]

[338] *Id.* at 1305:13-21; *see also* Plunkett Dep. at 146:11-21, ECF No. 9885, Ex. 34.
[339] Carson Hr'g Tr. at 1305:22-1307:10 (citing Carson Hr'g Slides at 21).
[340] *Id.* at 1401:17-22.
[341] *Id.* at 1305:1-4.
[342] *Id.* at 1305:5-9.

5. Frequency and duration of use are reliable and well-accepted ways to evaluate dose in epidemiology, and it is not necessary to know the exact amount of fibrous talc or heavy metals in TPP

J&J has argued that it is not possible to establish a causal link between TPP and ovarian cancer because we do not know the exact amounts of each constituent part that any given user is exposed to. As Dr. Carson explained, it is not necessary to know the exact amounts of metals in TPP because "these metals act as catalysts, and very small minute amounts of them have the full force and effect in distant tissues."[343] Nor is it necessary to know the specific amount of fibrous talc (or any other constituents, including asbestos) that reach the ovaries because once the carcinogens are lodged in the ovarian tissue for "a very long period of time," they will cause "inflammation at a minimum, and in some people ovarian cancer."[344]

Regardless, Dr. Carson did consider dose in terms of cumulative dose (frequency) over time (duration), a "very useful and well tried and accepted principle of how to do dosing in epidemiology."[345] Absent specific, reliable dose measurements, "we often will use surrogates such as frequency and duration," much like the use of "pack years" to evaluate an individual's cigarette exposure.[346] For example, it is generally accepted and understood that cigarette use causes lung

[343] *Id.* at 1443:8-18.
[344] *Id.* at 1452:1-12.
[345] *Id.* at 1457:23-1458:14.
[346] *Id.* at 1458:4-14.

cancer in some users despite the fact that there is no precise, individual dose calculation of the nicotine and other chemicals in cigarettes.[347] Indeed, the Hill dose-response analysis looks at duration and frequency of exposure of the entire product with reference to the epidemiological data as a whole.[348] The PSC contends that TPP as a whole—the mixture of all constituent parts, including fibrous talc and heavy metals—cause ovarian cancer, not any single constituent part acting alone. Accordingly, considering dose with reference to frequency and duration is an acceptable and reliable method for TPP, and, like cigarettes, it is not necessary to know the exact amount of fibrous talc and heavy metals present in TPP.

VII. CONCLUSION

The opinions of the PSC's experts are admissible under Fed. R. Evid. 702 and *Daubert*. The PSC's experts are all unquestionably qualified to provide their opinions in this case.

Additionally, the PSC's experts' opinions on general causation are based on a proper methodology, including the analysis of the totality of the epidemiologic literature relevant to the question of whether TPP is associated with ovarian cancer. The PSC's experts properly analyzed the strengths and weaknesses of all studies and sufficiently addressed J&J's critiques of the literature, including whether recall bias

[347] *Id.* at 1458:15-23.
[348] *See* ECF No. 9914 at 157-160.

or confounding were responsible for the reported association, particularly in light of the consistent increased risk across studies with serous ovarian cancer specifically. The PSC's experts also reliably applied the Hill Guidelines to the totality of the evidence. The PSC's experts' opinions regarding the strength and consistency of the risk ratios in the epidemiologic data are based on reliable methodology and appropriately identify consistent risk ratios above 1.0 across studies. They also opine based on sufficient and reliable data that there is evidence of a dose-response.

The PSC's experts also provided reliable opinions on biologic plausibility based on a methodology that all parties' experts agree on. They relied on sufficient evidence demonstrating that the association between genital use of TPP and ovarian cancer "makes sense" – that TPP can reach the ovaries, fallopian tubes, and peritoneal surfaces (by migration or inhalation), and once there, can cause chronic inflammation, oxidative stress, and ROS, which can lead to cancer in some women.

Dr. Saed's opinions are based on sound methodology, are consistent with research conducted by other scientists, and establish a biologically plausible mechanism by which TPP causes ovarian cancer. As to Dr. Longo's testing for asbestos and fibrous talc in historical J&J talcum powder samples, J&J concedes he used reliable methodologies. Any objections to his application of those methods are matters for the jury in analyzing the weight of his opinions, not admissibility. Finally, the PSC's experts' opinions on the presence of carcinogens in TPP including

asbestos, fibrous talc, and heavy metals, and the carcinogenic effect of those constituents on the human body, are based on reliable evidence and provide further evidence of biologic plausibility.

For the foregoing reasons, J&J's motion to exclude the general causation opinions of the PSC's expert witnesses should be denied in full.

Respectfully submitted,

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