FILED
SEP 2 2016
ELSON C. JOHNSON, J.S.C.

COURT INITIATED

BRANDI CARL **PLAINTIFF** **V.** **JOHNSON & JOHNSON, ET AL.** **DEFENDANT**	**SUPERIOR COURT OF NEW JERSEY** **LAW DIVISION: ATLANTIC COUNTY** **DOCKET NO.: ATL-L-6546-14** **CIVIL ACTION NO.: 300 (MCL)** **TALC-BASED POWDER PRODUCTS LITIGATION**
DIANA BALDERRAMA **PLAINTIFF** **V.** **JOHNSON & JOHNSON, ET AL.** **DEFENDANT**	**SUPERIOR COURT OF NEW JERSEY** **LAW DIVISION: ATLANTIC COUNTY** **DOCKET NO.: ATL-L-6540-14** **CIVIL ACTION NO.: 300 (MCL)** **TALC-BASED POWDER PRODUCTS LITIGATION**

ORDER

THIS MATTER having come before the court on Defendants' motions to bar expert testimony; and Defendants having filed companion motion(s) for summary judgment seeking dismissal of Plaintiffs' Complaints in the event the motion(s) to bar testimony are granted; and Plaintiffs having filed cross motions to bar Defendants' expert testimony; and the court having conducted a plenary hearing on August 8, 9, 11, 12, 15, 16, and 19, 2016, at which time the court heard from Mark C. Haggerty, Esquire, Michael R. Klatt, Esquire, Gene M. Williams, Esquire, Susan M. Sharko, Esquire, Julie Tersigni, Esquire, Lorna Dotro, Esquire, Hunter K. Ahern, Esquire, Kenneth J. Ferguson, Esquire, and Ann Thorton Field, Esquire, on behalf of Defendants in support of their application; and Plaintiffs opposing this motion, Richard Golomb, Esquire, Ruben Honik, Esquire, Ted G. Meadows, Esquire, David B. Dearing, Esquire, Timothy W. Porter, Esquire, Michelle Parfitt, Esquire, and Paul R. D'Amato, Esquire, appearing; and the court having received expert testimony and oral argument of counsel conducted pursuant to *Evid. R.* 104 and 702, the standards articulated by our Supreme Court in *Kemp vs. The State of New Jersey* 174 *N.J.* 412 (2002), and for the reasons stated in the Opinion of even date herewith; and for good cause shown;

IT IS ON THIS 2nd DAY OF SEPTEMBER, 2016, **ORDERED** as follows:

1. Defendants' motion to bar the testimony of Dr. Graham A. Colditz is hereby GRANTED.

2. Defendants' motion to bar the testimony of Dr. Daniel W. Cramer is hereby GRANTED.

3. As a consequence of the aforesaid rulings, Defendants' motion for summary judgment as to Plaintiff, Brandi Carl, is hereby GRANTED. Plaintiff, Carl's Complaint is dismissed with prejudice.

4. As a consequence of the aforesaid rulings, Defendants' motion for summary judgment as to Plaintiff, Diana Balderrama, is hereby GRANTED. Plaintiff, Balderrama's Complaint is dismissed with prejudice.

5. As a consequence of the aforesaid rulings, Defendants' motions to bar testimony of other expert witnesses are deemed MOOT.

6. As a consequence of the aforesaid rulings, Plaintiffs' cross-motions to bar Defendants' experts are deemed MOOT.

Nelson C. Johnson 9-2-16

NELSON C. JOHNSON, JSC

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OF THE COMMITTEE ON OPINIONS

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OPINION

RE: KEMP HEARINGS
DECIDED: SEPTEMBER 2, 2016

APPEARANCES:
RICHARD GOLOMB, ESQUIRE, PLAINTIFF
RUBEN HONIK ESQUIRE, PLAINTIFF
PAUL R. D'AMATO, ESQUIRE, PLAINTIFF
TED G. MEADOWS, ESQUIRE, PLAINTIFF
DAVID B. DEARING, ESQUIRE, PLAINTIFF
TIMOTHY W. PORTER, ESQUIRE, PLAINTIFF
MICHELLE PARFITT, ESQUIRE, PLAINTIFF

GENE M. WILLIAMS, ESQUIRE, DEFENDANT
SUSAN M. SHARKO, ESQUIRE, DEFENDANT
JULIE TERSIGNI, ESQUIRE, DEFENDANT
MICHAEL R. KLATT, ESQUIRE, DEFENDANT
LORNA DOTRO, ESQUIRE, DEFENDANT
HUNTER K. AHERN, ESQUIRE, DEFENDANT
KENNETH J. FERGUSON, ESQUIRE, DEFENDANT
MARK C. HEGARTY, ESQUIRE, DEFENDANT
ANN THORTON FIELD, ESQUIRE, DEFENDANT

NELSON C. JOHNSON, J.S.C.

HAVING CAREFULLY REVIEWED THE MOVING PAPERS AND RESPONSES FILED, I HAVE RULED ON THE ABOVE CAPTIONED MATTERS AS FOLLOWS:

I. POSTURE OF ISSUES BEFORE THE COURT

This matter is before the court on the motion of the Defendants, Johnson & Johnson and Imerys Talc America, Inc. (hereinafter referred to collectively as "Defendants") seeking relief against Brandi Carl and Diana Balderrama (hereinafter the "Plaintiffs"), both of whom brought claims alleging that a talc-based product manufactured by Defendants has caused each of them to develop ovarian cancer.

These two lawsuits were filed in the Superior Court of New Jersey, Atlantic County; the *Carl* matter on November 17, 2014 and the *Balderamma* matter on November 25, 2014. Pursuant to *R.* 4:38A, on October 20, 2015, the Supreme Court designated this litigation as a Multi-County Litigation (MCL), to receive centralized management by this court. The court is confident that, in these matters, every avenue of legal and scientific research has been explored by capable legal counsel and learned scientists, and that the litigants' interests have been well represented.

Presently before the court is a challenge brought by Defendants to Plaintiffs' contention that the use of talc-based products caused them to develop ovarian cancer; said challenge was brought by motions to bar testimony of each of Plaintiffs' several expert witnesses. [NOTE: Defendants have filed companion motion(s) for summary judgment seeking dismissal of Plaintiffs' Complaints in the event the motion(s) to bar testimony are granted.] Defendants' challenge to Plaintiffs' experts was heard, and expert testimony, together with legal briefs and oral argument of counsel, were received by the court at a plenary hearing conducted pursuant to the standards articulated by the Supreme Court in *Kemp v. State of New Jersey,* 174 *N.J.* 412 (2002), (hereinafter a "*Kemp* Hearing") as required by *Evid. R.* 104 and consistent with *Evid. R.* 702. The court conducted said hearing on August 8, 9, 11, 12, 15, 16, and 19, 2016.

Defendants argue that Plaintiffs' hypotheses as to both general and specific causation are flawed; that there is no reliable scientific evidence to support Plaintiffs' contentions; and that accordingly, Plaintiffs' experts must be barred from testifying at trial. In reply, Plaintiffs argue that their experts are qualified by education, training, and experience and that their opinions are

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reliable because they are based on a sound scientific methodology, involving the type of information relied upon by experts in their field.

Thus, in evaluating the totality of the evidence presented by Plaintiffs, the question before the court may be stated as follows: Have Plaintiffs shown that their experts' theories of causation are sufficiently reliable as being based on a sound, adequately-founded scientific methodology, *to wit*, that they are based upon methods upon which experts in their field would reasonably rely in forming their own (possibly different) opinions about the cause(s) of each of Plaintiffs' ovarian cancers?

Courts are experts in the law, not science. This court's review "is as broad as the breadth of the proffer and the challenges thereto that the parties present." *Hisenaj v. Kuehner*, 194 *N.J.* 6, 19 (2008). Accordingly, this court's role is that of a "gatekeeper" who – based upon the proofs presented by the parties - must assess whether or not the hypotheses of causation advanced by Plaintiffs' experts are sufficiently reliable to be presented to a jury.

II. SCIENTIFIC STUDIES

Prior to receipt of testimony from the parties' experts, the court solicited from counsel the submission of all reports, abstracts, epidemiology studies, and peer-reviewed articles ("treatises" or "scientific literature") that were relied upon by the witnesses in formulating their opinions. That process began several months prior to the *Kemp* Hearing. As a result, approximately 100 treatises relating to talc, cancer, and miscellaneous related scientific issues were reviewed by the court both prior to and during the hearing. The court is grateful to counsel for these submissions; they were invaluable in preparing for the hearing and analyzing the evidence presented. [NOTE: Accompanying this ruling are Appendices A thru E which catalogue a portion of the peer-reviewed articles discussed at the hearing, together with public pronouncements by agencies possessing authoritative knowledge on cancer.]

Of particular value to the court in making its analysis is *The Reference Manual on Scientific Evidence* (3rd Edition, hereinafter, "the *Reference Manual*") issued by the Federal Judicial Center and the National Research Council of the National Academies. The *Reference Manual* is an invaluable tool. Because it is indicative of what the scientific community deems to be reasonable, the *Reference Manual* provides excellent guidance to trial judges in sifting through and prioritizing

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the information generated at a *Kemp* Hearing. At such a hearing, a court is asked to assess whether the experts in the field would reasonably rely on methods and data as Plaintiffs' experts have done in this case. Through the *Reference Manual*, the scientific community "speaks" to trial courts, and advises as to what may be considered to be reasonable, from an informed and objective perspective.

III. INITIAL FINDINGS RE: EXPERT WITNESSES

Based upon consideration of the experts' written submissions and a careful review of all witnesses' testimony, together with the court's reading of the learned scientific treatises referenced herein, the court makes the following findings:

A. Expert Witnesses

The nine witnesses who testified at the *Kemp* Hearing are exceptionally learned and accomplished professionals; their credentials are impressive. No serious challenge was made to the qualifications of any witness. The court benefited greatly from their testimony. A brief profile of each witness follows:

Witnesses for Plaintiffs

(1) Graham A. Colditz, M.D., MPH, DRPH, FAFPHM: Dr. Colditz trained in Medicine at the University of Queensland, obtaining a M.B., B.S. degree. He trained in Epidemiology at Harvard School of Public Health, obtaining a Master of Public Health degree and subsequently a Doctorate. Dr. Colditz is the Niess-Gain Professor of Medicine at Washington University School of Medicine and the Associate Director, Prevention & Control, at the Alvin J. Siteman Cancer Center. He is the Chief of the Division of Public Health and Sciences in the Department of Surgery at Washington University School of Medicine. Dr. Colditz also serves as co-director of the Biostatistics Core for the Siteman Cancer Center. Dr. Colditz was presented on the issue of general causation of ovarian cancer.

(2) Daniel W. Cramer, M.D., Sc.D.: Dr. Cramer received his M.D. degree from the University of Colorado School of Medicine and a Doctor of Science degree in Epidemiology from the Harvard School of Public Health. Dr. Cramer is a Professor of Obstetrics, Gynecology and Reproductive Biology at Brigham and Women's Hospital, Harvard Medical School, and Professor of Epidemiology at the Harvard T.H. Chan School of Public Health. He heads the Research

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Division of the OB-GYN Epidemiology Center, doing research in the field of environmental and genetic risk factors for a variety of obstetrical and gynecologic problems with a particular focus on ovarian cancer. Dr. Cramer was presented on the issues of both general and specific causation of ovarian cancer.

(3) John J. Godleski, M.D.: Dr. Godleski received his M.D. degree from the University of Pittsburgh School of Medicine. He is a Professor of Pathology at Harvard Medical School, Brigham and Women's Hospital, and a Professor of Environmental Health at Harvard TH Chan School of Public Health. Dr. Godleski has published more than 160 papers related to pulmonary/environmental pathology including a number using analytical electron microscopy. He currently leads the Particles Research Core in the Harvard-NIEHS Environmental Research Center and serves as Associate Director of the Harvard Clean Air Research Center supported by the US Environmental Protection Agency. Dr. Godleski was presented on the identification of particles, and on the issue of specific causation of ovarian cancer.

(4) Curtis J. Omiencinski, Ph.D., ATS: Dr. Omiencinski is an elected fellow and professor in the Academy of Toxicological Sciences and a Professor and the H. Thomas and Dorothy Willits Hallowell Chair in the Center for Molecular Toxicology & Carcinogenesis and the Department of Veterinary and Biomedical Sciences, College of Agricultural Sciences, at The Pennsylvania State University. He received his B.S. degree from the State University of New York at Albany and his Ph.D. degree in Pharmacology from the University of Washington's School of Medicine. He has authored more than 115 peer-reviewed papers and has published over 30 reviews, book chapters and other reports in the areas of pharmacology, molecular biology, toxicology, cancer research and genetics. His testimony was presented in connection with Plaintiffs' hypothesis of biologic causation of ovarian cancer.

(5) David C. Steinberg, MBA, FRAPS: Mr. Steinberg owns a regulatory consulting firm for the cosmetic industry, specializing in the chemistry of cosmetic ingredients, preservatives and preservation, international and U.S. cosmetic regulations, and marketing of raw materials. He received his B.S. degree in Chemistry from Drexel University and an MBA Management degree from Pace University. He is a Fellow for the Regulatory Affairs Professionals Society.

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Witnesses for Defendants

(1) Lewis A. Chodosh, M.D., Ph.D.: Dr. Chodosh is a physician and cancer researcher. He graduated *summa cum laude*, Phi Beta Kappa from Yale University with Distinction in Molecular Biophysics and Biochemistry. He received his M.D. degree from Harvard Medical School, graduating *magna cum laude* and his Ph.D. degree in Biochemistry from the Massachusetts Institute of Technology. Dr. Chodosh currently serves as Chairman of the Department of Cancer Biology and is a Professor in the Department of Cancer Biology and in the Department of Medicine in the Division of Endocrinology, Diabetes and Metabolism at the University of Pennsylvania School of Medicine. He also serves as Associate Director for Basic Science in the Abramson Cancer Center at the University of Pennsylvania, as well as the Director of Cancer Genetics at the Abramson Family Cancer Research Institute. Dr. Chodosh testified as to the diverse means by which cancer(s) develop in the human body and challenged the fundamental bases of Plaintiffs' biological hypothesis and contentions regarding specific causation.

(2) Mary J. Cunningham, M.D.: Dr. Cunningham is a board-certified gynecologic oncologist with GynOncology of Central New York in Syracuse, New York. She received her M.D. degree from Northwestern University Medical School. Dr. Cunningham serves as a Professor in the Department of Obstetrics and Gynecology and Director of the Division of Gynecologic Oncology at the State University of New York Upstate Medical University. She is a member of the American Congress of Obstetricians and Gynecologists and the Society of Gynecologic Oncology and the Principal Investigator for with the NRG Oncology cooperative trial group. Dr. Cunningham was presented in opposition to the testimony of Dr. Colditz and Dr. Cramer.

(3) Elaine F. Schumacher: Ms. Schumacher is a Senior Research Scientist and Analytical Microscopist with McCrone Associates, Inc. of Westmont, Illinois. She received her B.S. degree in Chemistry from Elmhurst College. Ms. Schumacher is a member of Microscopy Society of America, Midwest Microscopy and Microanalysis Society, Microanalysis Society and American Chemical Society. In addition, she has authored several publications on the application of microscopy. Ms. Schumacher was presented in opposition to the testimony of Dr. Godleski.

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(4) Douglas L. Weed, M.D., M.P.H., Ph.D.: Dr. Weed serves as a member of the Ethics Committee of the American College of Epidemiology. He received his B.S. and M.D. degrees from Ohio State University and his Ph.D. and M.P.H in Epidemiology degree from the University of North Carolina at Chapel Hill. Dr. Weed has 25 years of service at the National Cancer Institute ("NCI") and serves as a Visiting Professor at numerous universities. He is the Review Editor of the Journal of the NCI and a peer reviewer for many medical journals in the field of epidemiology. Dr. Weed has authored more than 30 peer-reviewed papers on causation methodology and systematic reviews, as well as meta-analyses of cancer epidemiology studies. Dr. Weed was presented in opposition to the testimony of Dr. Colditz and Dr. Cramer.

IV. CASE LAW PERTINENT TO THE COURT'S ANALYSIS

As confirmed by the case law cited hereinafter, New Jersey's courts recognize that litigants claiming that they were harmed by the use of a product may never recover if they must await general acceptance by the scientific community of a reasonable, but not as yet certain, theory of causation linking the harm claimed to the product ingested. Because of our courts' concern that – despite compelling indicators linking a product to the harm – plaintiffs may never recover for their injuries, there are situations in which a theory of causation that has not yet reached general acceptance in the scientific community may still be found sufficiently reliable to support submission of such a claim to a jury.

In his learned essay first published in the *New Jersey Law Journal* on May 5th and 12th of 1988 (*see* 121 *N.J.L.J.* Index Page 882, *et seq.*), Justice Handler noted that "...there are many new classes of litigation, such as those involving exposure to toxic contaminants, asbestos and carcinogens, that pose complicated and novel problems." Justice Handler noted the "warfare" in our courtrooms is oftentimes resolved by the testimony of experts from diverse fields of knowledge:

> The point is that there is no difference in the treatment of testimony of social scientists and psychologists, on the one hand, and chemists or biologists, on the other. Differences in acceptability have more to do with expanding frontiers of scientific knowledge.
>
> 121 *N.J.L.J.* Index at 883.

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Until the final decade of the 20th Century, the time-honored test for the admissibility of expert testimony based upon a body of knowledge peculiar to a field of scientific study was that it had to be generally accepted or had been accepted by at least a substantial minority of the scientific community. *See Frye v. United States,* 54 *App. D.C.* 46 (D.C. Cir. 1923). In *Rubanick v. Witco Chem. Corp.,* 125 *N.J.* 421, 432 (1991), our Supreme Court modified that test with regard to evidence proffered for use in toxic tort cases. The Court held that a less stringent test than the general acceptance test should apply with regard to "new or developing theories of causation in toxic-tort litigation." *Id.* at 432. In writing for the Court, Justice Handler spoke of a methodology based test, that is, if the methodology by which the expert reached a conclusion is sound, the conclusion may be introduced into evidence. *Id.* at 438-40.

Pursuant to *Rubanick,* the key to reliability is the determination that the expert's opinion is based on a "sound, adequately-founded scientific methodology involving data and information of the type reasonably relied on by experts in the scientific field." *Id.* at 449. In order to be *valid methodology* (*viz.*, accepted by others in the scientific community), the expert's opinions must be supported by "prolonged, controlled, consistent, and validated experience." *Id.* at 436.

As this court understands *Rubanick,* in determining whether a scientific methodology is valid, trial courts must consider whether other scientists in the field use similar methodologies in forming their opinions and also should consider other factors that are normally relied upon by medical professionals. The appropriate inquiry is not whether the court thinks that the expert's reliance on the underlying data was reasonable, but rather whether comparable experts in the field would actually rely on that information. With regard to evaluating the testimony of knowledgeable experts in order to determine the acceptability of a theory, the *Rubanick* Court cautioned trial courts to attend to "the hired gun phenomenon," *i.e.*, that an expert can be found to testify to the truth of almost any factual theory or to disagree with almost any theory and to discount the research of others. *Rubanick, supra* at 453 (citations omitted).

Following *Rubanick,* in *Landrigan v. Celotex Corp.,* 127 *N.J.* 404 (1992), *Caterinicchio v. Pittsburgh Corning Corp.*, 127 *N.J.* 428 (1992), and *Dafler v. Raymark Industries, Inc.*, 259 *N.J. Super.* 17, 36 (App. Div. 1992), *aff'd. o.b.,* 132 *N.J.* 96 (1993), the Court held that experts relying on epidemiological studies could provide sufficient reliable evidence for the causes of diseases in specific individuals to present the issue of causation to juries. *Landrigan* and *Caterinicchio*

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involved the relationship of asbestos to colon cancer; *Dafler* addressed the relationship of cigarette smoking and asbestos to lung cancer.

In *Landrigan,* an occupational asbestos exposure case, the trial court dismissed the case on the ground that there was a lack of medical evidence to establish asbestos exposure as the cause of the disease. The Appellate Division affirmed. The Supreme Court reversed and held that epidemiologists could help juries determine causation in toxic tort cases and rejected the proposition that epidemiological studies must show a relative risk factor of "2.0" before gaining acceptance by a court. *Landrigan, supra* at 419. (A discussion of epidemiology and relative risk begins at p. 12).

The Supreme Court in *Landrigan* ruled that a trial judge must consider all the scientific data, sources thereof, and the methodology by which an expert reaches a conclusion, "includ[ing] an evaluation of the validity both of the studies on which he relied and of his assumption that the decedent's asbestos exposure was like that of the members of the study populations." *Id.* at 420. Additionally, the Supreme Court advised that "to determine the admissibility of the witness's opinion, [a] court, without substituting its judgment for that of the expert, should examine each step in [the expert's] reasoning." *Id.* at 421.

During the *Kemp* Hearing in these proceedings the court invited counsel to research what other courts have done on a relative risk factor of less than "2.0" and to submit their findings. The briefs furnished and the case law cited were very helpful. In reviewing the case law submitted by counsel, it is apparent that most courts across the nation – federal and state alike – discourage a dogmatic insistence upon a showing of a relative risk factor of "2.0" to support general causation. This court shares that perspective.

One case, cited by both sides, provided valuable guidance, namely *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 *F. Supp.* 2d 584 (D.N.J. 2002), *aff'd*, 68 F. Appx. 356 (3d Cir. N.J. 2003). The court in *Magistrini* noted "[a]s a general matter, the Rules of Evidence 'embody a strong and undeniable preference for admitting any evidence' that could potentially assist the trier of fact and Rule 702 is liberally interpreted by the district courts." *Id.* 595 (citations omitted). *New Jersey Evidence Rule* 702 is identical to the Federal Rule. That said, the court in *Magistrini* also cautioned, "[t]he Court's inquiry 'must be solely on principles and methodology, not on the conclusions that they generate.'" *Id.* (citing *Daubert v. Merrell Dow Pharms.*, 509 *U.S.* 579, 595

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(1993)). In articulating the mental process of the "gatekeeper," the court in *Magistrini* cited the Supreme Court decision in *GE v. Joiner,* 522 *U.S.* 136 (1997), wherein Chief Justice Rehnquist advised trial judges:

> But conclusions and methodology are not entirely distinct from one another. Trained experts commonly extrapolate from existing data. But nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered.
>
> *Id.* at 146.

A reading of the case law as to the weight attached to a relative risk factor of less than "2.0" shows that it is only one of the factors to be considered by the court. What must also be examined are the foundational sources of the expert's opinions. As discussed herein (see p. 17) in connection with the court's examination of the "Bradford Hill" criteria, although no single criterion is dispositive, research performed prior to litigation and peer-reviewed essays on the scientific issue at hand are the basic means by which to demonstrate reliability. Where neither exists, an expert witness is obligated to explain to the court how she/he proceeded in arriving at his/her conclusions by referencing some objective source(s), *e.g.*, a peer-reviewed article in a reputable medical/science journal, the public pronouncements of an agency with respected authority on the issue, or a learned treatise on the issue, in order to demonstrate that she/he has followed the scientific method at the standard maintained by some recognized minority of scientists in his/her area of science.

Accordingly, as this court understands New Jersey law and our Supreme Court's holding in *Landrigan,* the admissibility of expert testimony in toxic tort cases "depends on the expert's ability to explain pertinent scientific principles and to apply those principles to the formulation of his or her opinion. Thus, the key to admission of the opinion is the validity of the expert's reasoning and methodology." *Landrigan, supra* at 414. Nonetheless, the Supreme Court noted that, traditionally, "plaintiffs have established a connection between tortious conduct and personal injuries through the testimony of medical experts who testify that the defendant's specific conduct was the cause of the plaintiffs' injuries[,]" but that "[t]oxic torts, however, do not readily lend themselves to proof that is so particularized." *Id.* at 415. Accordingly, plaintiffs in toxic tort cases

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"may be compelled to resort to more general evidence, such as that provided by epidemiological studies." *Id.* This court is, of course, bound by the holding in *Landrigan* that "when an expert relies on such data as epidemiological studies, the trial court should review the studies, as well as other information proffered by the parties, to determine if they are of a kind on which such experts ordinarily rely." *Id.* at 417. (In the course of analyzing the issues raised herein, the court has carefully read every epidemiological study cited by the witnesses and legal counsel at the *Kemp* Hearing).

Ten years after *Landrigan,* in *Kemp v. State of New Jersey,* 174 *N.J.* 412, 430-32 (2002), the Supreme Court applied the *Rubanick* standard to a case involving an injury allegedly caused by vaccination, and implied its applicability to all tort cases in which a medical cause-effect relationship has not yet been confirmed by the scientific community but for which "compelling" evidence suggests that such a relationship does exist. In *Kemp,* the Supreme Court suggested that an *N.J.R.E.* 104 hearing is the preferred procedural practice in every case involving an expert's theory that has not yet achieved "general acceptance," finding that the trial court has an obligation, *sua sponte*, to conduct such a hearing and that the failure to do so is plain error.

Accordingly, from this court's perspective, the inquiry at a *Kemp* Hearing must be "flexible." Its focus must be on principles and methodology and not necessarily on the conclusions/opinions that such scientific methodology may generate. The trial court's role is to determine whether the expert's opinion is derived from a sound and well-founded methodology. "There must merely be *some expert consensus* that the methodology and the underlying data are generally followed by experts in the field." *Rubanick, supra* at 450 (Emphasis added). Thus, at this *Kemp* Hearing, Plaintiffs' burden is to demonstrate that the methodologies used by their experts are consistent with valid scientific principles accepted in the scientific and medical communities.

Finally, the court is guided by the words of Justice Handler in *Rubanick, supra,* 125 *N.J.* 451, wherein he cautioned trial court judges that they must exercise restraint.

> We do not believe that in determining the soundness of the methodology the trial court should directly and independently determine as a matter of law that a controversial and complex scientific methodology is sound. The critical determination is whether comparable experts accept the soundness of the

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methodology, including the reasonableness of relying on this type of underlying data and information. *Great difficulties can arise when judges, assuming the role of scientist, attempt to assess the validity of a complex scientific methodology.*

(Emphasis added).

V. "BUILDING BLOCKS" OF THE SCIENTIFIC METHOD RELEVANT TO TALC-BASED POWDER AND OVARIAN CANCER

A *Kemp* Hearing is the intersection of the scientific method and the rule of law. If our court system is to be respected by the scientific community, then we must respect the scientific process. Essentially, the scientific method is the systematic pursuit of knowledge. This pursuit consists of those principles and procedures involved in the recognition and formulation of a problem, the collection of data through observation and experimentation, and the articulation and testing of a hypothesis by which to resolve the problem, and hopefully gain new knowledge useful to society.

What follows are the "building blocks" of the scientific method which the court must consider in evaluating Plaintiffs' experts' methodologies in arriving at their conclusions and opinions, and whether the same are "reliable." The key is consistent adherence to the scientific method. In addressing the issues to be resolved, the court has endeavored to faithfully apply the principles and tools of science to the issues at hand.

A. Epidemiological Studies

The two primary types of observational studies relevant to these proceedings (*viz.*, epidemiology studies) are (1) cohort studies, and (2) case-control studies. Cohort studies compare the incidence of disease among individuals exposed to a substance with an unexposed group. Case-control studies examine the frequency of exposure in individuals who presently have the disease and compare them to a group of individuals who do not have the disease.

Epidemiologic studies provide "the primary generally accepted methodology for demonstrating a causal relation between a chemical compound and a set of symptoms or disease." See *Conde v. Velsicol Chem. Corp.*, 804 *F. Supp.* 972, 1025–26 (S.D. Ohio, 1992), *aff'd.*, 295 *F. 3d* 1194 (11th Cir. 2002). When a scientific rationale doesn't exist to explain logically the biological mechanism by which an agent causes a disease, courts may consider epidemiologic

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studies as an alternate means of proving general causation. According to the *Reference Manual*, at page 723-24, large epidemiological studies present some of the strongest medical/scientific evidence. The typical use of large population-based studies is in connection with "general causation." As noted in the *Reference Manual* at page 623, general causation is concerned with "whether an agent increases the incidence of disease in a group and not whether the agent caused any given individual's disease." Nonetheless, the *Reference Manual* at page 552 cautions trial judges that "it should be emphasized that *an association is not equivalent to causation.*" (Emphasis in the original text).

Epidemiologic studies attempt to identify agents that are associated with an increased risk of disease. Thus, the first question an epidemiologist must ask is whether or not an association exists between exposure to a substance and a particular disease. An association between exposure to an agent and a disease exists when the two occur together more frequently than they would by mere chance. In that situation, the association is referred to as *significant.* "Statistically significant" means that the scientific community recognizes that the association between two or more variables is caused by something other than "random chance." Once a significant association is observed, the scientist undertaking the study must assess the *strength* of the association, plus whether the reason for the observed association is due to *bias, chance or a genuine effect.* A measure of the strength of an association in an epidemiological study can be expressed in terms of its "relative risk" (hereinafter "R/R"). R/R indicates the difference in the risk of contracting a disease in people exposed to a substance, as compared to those who are unexposed but are otherwise similar, in this case the American adult female population. Determining the R/R is important in understanding the results of a study because virtually every disease associated with a risk factor also occurs, at some rate, in the general population among study participants who are unexposed to the risk factor.

R/R is commonly calculated by dividing the risk of developing a disease observed in an exposed group by the risk observed in an unexposed, but otherwise similar, group. If the risks of the unexposed and exposed are the same, then the relative risk estimate (which mathematically is simply the former divided by the latter) is "1.0", also termed "null." The null value indicates that exposure is not associated with the disease in that study. Thus, an R/R of "1.0" means that the agent has no effect on the incidence of disease. Similarly, if the R/R estimate is "1.3," then risk

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appears to be 30% higher among the exposed compared to the non-exposed. When an R/R reaches "2.0," the risk has doubled, indicating that the risk is twice as high among the exposed group as compared to the unexposed group. As discussed in the *Reference Manual* at page 612, note 192, there exists "... considerable disagreement on whether a relative risk of 2.0 is required or merely a taking-off point for determining sufficiency ...".

In evaluating epidemiological studies, it is important to note that "[a]n association is not equivalent to causation. An association identified in an epidemiological study may or may not be causal. Assessing whether an association is *causal* requires an understanding of the strengths and weaknesses of the study's design and implementation, as well as a judgment about how the study findings fit with other scientific knowledge." *Reference Manual* at page 552-3. As cautioned by the *Reference Manual,* the closer the R/R is to the null (or the further it is from 2.0), the greater the concern for bias or confounding.

Generally, there are three reasons that a positive association may be observed: (a) bias (including confounding factors), (b) chance, and (c) real effect. Each must be evaluated to extract a valid message from the study. Evaluation of these factors measures the "internal validity" of an epidemiology study, *viz.*, the extent to which a particular study's findings are viable and sound. "Bias" in epidemiology is systematic error, which includes "confounding bias." The underlying impact of these biases is to make the two groups being compared different in more ways than just the variable being studied. Sources of bias must be considered in interpreting an epidemiological study because bias can produce an erroneous association. *Reference Manual* at pages 591-3.

The record of the *Kemp* Hearing conducted by the court is replete with testimony, argument, and legal briefs regarding the significance to be attached to various studies conducted by epidemiologists on the possible association of talc-based products and ovarian cancer. Each side cited numerous studies to support its position. Nevertheless, this court's review of the various studies is informed by the admonishment of the *Reference Manual* at page 576:

> Common sense leads one to believe that a large enough sample of individuals must be studied if the study is to identify a relationship between exposure to an agent and disease that truly exists. Common sense also suggests that by enlarging the sample size (the size of the study group), researchers can form a more accurate conclusion and reduce the chance of random error in their results...With large numbers, the outcome of test is less likely to be influenced by random error, and the researcher would have greater confidence in the inferences drawn from the data.

B. Laboratory Studies on Talc and Cancer

To confirm a possible cause-and-effect relationship suggested by epidemiological studies, an exposure assessment can be conducted in order that the findings of those studies may be compared to the adverse health impacts predicted from exposure estimates and toxicological data from laboratory experiments.

Laboratory studies can be conducted using cells from animals or humans. Research involving a controlled environment, such as cell cultures in a test tube or in a petri dish, are called *in vitro* studies. Studies done on living organisms are called *in vivo* studies. There are many institutions around the world conducting laboratory studies focused upon the potentially causal relationship between various substances and cancer. Much can be learned from those studies.

Here, regarding Plaintiffs' claim of a specific causal relation between talc-based powder and ovarian cancer, laboratory studies can be performed on both human and animal cells to assess the impact of talc upon tissue and cells removed from both women and animals.

C. Cancer Biology and Research

The past generation has seen large strides made in understanding the pathways which cause human cancers. These "pathways" are essentially a molecular chain of events that cause human cancers. Scientists now have the ability to analyze many thousands of genes, and to study how a particular gene responds to various substances. This can be done in both human and animal cells, both *in vitro* and *in vivo*. In the process scientists can gain a better understanding of what triggers cancer. Thus, understanding how these pathways get turned on or turned off by the mutations in key genes is critical to understanding the rudimentary causes of cancer. As will be discussed hereinafter in connection with the testimony of Dr. Lewis Chodosh, there is a great deal to be learned from studying the biology of cancer. The biology of cancer and the research being done (and results from years past) are all relevant to any scientific inquiry into the alleged causal connection between talc-based powder and ovarian cancer.

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D. Animal Studies

Another means by which to measure the toxicity of an agent in humans is through animal toxicology studies. The purpose of animal studies is not to predict what specific types of cancer a particular carcinogen might cause in humans, but rather to identify whether it can cause cancer at all. However, animal studies are of limited use in determining whether a particular substance causes a particular disease, or type of cancer, in humans. Generally, where both epidemiologic studies and animal toxicology are available, there is no universal rule for how to reconcile them. The scientific method dictates that careful assessment of the methodological validity and power of the epidemiologic evidence must be undertaken and the quality of the toxicological studies and the question of interspecies extrapolation and dose-response relationship must be also considered.

E. Agencies Which Study Cancer

Though cancer has plagued mankind throughout the history of civilization, it wasn't until the twentieth century that the U.S. Congress decided to take the lead in developing a permanent agency of government to encourage research into the causes and cures of cancer.

> In 1937, Congress established the National Cancer Act of 1937 to provide additional support for cancer research – it was the first time Congress had appropriated funds toward a non-communicable disease. The Act established the National Cancer Institute ("NCI") as the federal government's primary agency to address research and training needs for the cause, diagnosis, and treatment of cancer. NCI's responsibilities included (in part):
>
> - Conducting, coordinating, and promoting research and studies relating to the cause, diagnosis, treatment, and prevention of cancer.
>
> - Reviewing and approving grant applications to support promising cancer research.
>
> ...
>
> - Collecting, analyzing, and disseminating the results of cancer research conducted in the United States and in other countries.
>
> [The above can be found at: http://www.cancer.gov/about-nci-overview/history.]

In addition to the NCI, several other agencies and associations study and report to the public. As shown in Appendix E, those entities include: U.S. Food and Drug Administration,

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American Cancer Society, World Health Organization, International Agency Research on Cancer, and The American College of Obstetricians and Gynecologists. [NOTE: Each of these agencies has made public pronouncements which are inconsistent with, and/or unsupportive of Plaintiffs' claims that talc-based powder causes ovarian cancer.]

F. Bradford Hill Criteria

From the court's perspective, this "building block" is really the "mortar" for the scientific method. The Bradford Hill criteria should be acknowledged, either initially or by way of summary, in any discussion of the method(s) by which scientists seek new knowledge on a given scientific question. Because this court sees the criteria discussed below as "mortar" for building the conclusions in this analysis, it is the final item discussed.

In 1965, respected scientist and pioneer in medical statistics, Sir Austin Bradford Hill (1897-1991), made a speech before a group of colleagues wherein he attempted to articulate those essential benchmarks which the scientific community must consider in distinguishing between causal and non-causal explanations of observed associations. That speech is likely the most widely-published and quoted after-dinner speech delivered by a physician.

In determining whether an observed association between a chemical and a disease is causal (*i.e.*, general causation), Hill advised that scientists should be guided by various factors, which are often referred to as the "Hill criteria."

These factors include: (1) **strength** of association (*i.e.*, is the association strong and statistically significant?); (2) **consistency** of the relationship (*i.e.*, whether it has been repeatedly observed in other persons?) (3) **specificity** of association (*i.e.,* is there a particular association between the substance and the condition it purportedly causes?*)*; (4) **temporality** (are the cause and effect bound in time, or as Hill states, "which is the cart and which is the horse?); (5) **biological gradient** (does the association reveal a dose-response curve?); (6) **plausibility** (*i.e.*, whether there exists a biologically plausible *mechanism* by which the agent *could* cause the disease?); (7) **coherence** (does cause-and-effect interpretation of the data conflict with the history and biology of the disease?); (8) **experiment** (is the frequency of the associated events affected by reducing the amount of the suspected substance?); (9) **analogy** (should science anticipate similar results from a consideration of alternative explanations?). Here, regarding talc-based products and

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ovarian cancer, though most of the factors come in for consideration to varying degrees; this is particularly true factors 1, 2, 5, and 6. [NOTE: When, as here, the R/R is significantly less than "2.0", factor #6 is essential.]

Finally, it should be noted that it is unlikely that Hill intended that scientists should be inflexibly bound to his criteria. There is little doubt in the scientific community that he encouraged that the seven identified considerations be applied flexibly. That said, a final portion of his speech is worthy of quoting verbatim.

> All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. *That does not confer upon us a freedom to ignore the knowledge we already have*, or to postpone the action it appears to demand at a given time. (Emphasis added).

VI. PRELIMINARY OVERVIEW OF EXPERT TESTIMONY AND ANALYSIS OF THE TOTALITY OF THE EVIDENCE PRESENTED

This court is ever mindful of its role as a "gatekeeper" and the "great difficulties" that can arise for a trial judge in ruling on the admissibility of expert testimony. The analysis for determining what proofs may be presented to a jury must be in accordance with the standards expressed by our Supreme Court; that is the frame of reference by which the information presented by counsel and the experts must be scrutinized. The court had the opportunity to observe closely the nine expert witnesses presented by the parties. Much was learned from each witness; nonetheless, a preliminary observation sets the foundation for all that follows.

Throughout these proceedings the court was disappointed in the scope of Plaintiffs' presentation; it almost appeared as if counsel wished the court to wear blinders. Plaintiffs' two principal witnesses on causation, Dr. Daniel Cramer and Dr. Graham Colditz, were generally dismissive of anything but epidemiological studies, and within that discipline of scientific investigation they confined their analyses to evidence derived only from small retrospective case-control studies. Both witnesses looked askance upon the three large cohort studies presented by Defendants. As confirmed by studies listed at Appendices A and B, the participants in the three large cohort studies totaled 191,090 while those case-control studies advanced by Plaintiffs' witnesses, and which were the ones utilized in the two meta-analyses performed by Langseth and

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Terry, total 18,384 participants. As these proceedings drew to a close, two words reverberated in the court's thinking: "narrow and shallow." It was almost as if counsel and the expert witnesses were saying, *Look at this, and forget everything else science has to teach us.*

The *Reference Manual* expressly cautions against a narrow and shallow examination of the science supporting Plaintiffs' contentions. "The critical difference between cohort studies and case-control studies is that cohort studies begin with exposed people and unexposed people, while case-control studies begin with individuals who are selected based on whether they have the disease or do not have the disease and their exposure to the agent in question is measured." (p. 557). Additionally, Section IV. B. of the *Reference Manual* warns of bias, particularly "information bias" of the participants. "In a case-control study, potential information bias is an important consideration because the researcher depends on information from the past to determine exposure and disease and their temporal relationship." (p. 585).

Equally troubling is Plaintiffs' failure to address meaningfully the other fields of scientific inquiry – or "building blocks" - in support of their assertion of general causation, *e.g.*, laboratory studies on talc, cancer biology, and animal studies. Most critical is their failure to provide a coherent explanation to support their hypothesis for biologic plausibility, which is #6 of the Hill criteria, to wit, "plausibility".

Neither Dr. Cramer nor Dr. Colditz expressed much interest in explaining just how it is that talc-based powder supposedly causes cancer in the ovaries, or for that matter any part of the human anatomy. "Inflammation" was used almost as a talisman that supposedly explained everything the court needed to know. Stated in lay terms, Dr. Cramer's and Dr. Colditz's postulation, essentially, is as follows: *The talc flows upstream and lodges in the ovaries; it irritates cells in the ovaries, causes inflammation, which in turn causes immunosuppression, and the inescapable result is cancer.* Positing that premise (which the court does not), both witnesses ignore the fact that that Dr. Godleski conceded on cross examination that he did not observe inflammation in any of the tissue –of either Plaintiff - that he examined.

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Q Doctor, you agree also that neither Mrs. Carl nor Mrs. Balderrama's treating pathologists noted any talc-related inflammatory reactions in their reports in these cases?

A That's correct.

(See generally the testimony of 8/9/16; see P129, L1 thru P130, L21).

A cornerstone of the "talc causes cancer" hypothesis is "inflammation," yet none was present in any of the tissue samples studied.

Incident to the meager width and depth of the investigation employed by Plaintiffs' experts in this litigation was the failure to address several questions arising from the proffered evidence. These questions illustrate the flaws in the methodology of Plaintiffs' experts.

1. Those epidemiological studies showing a potential link between talc-based powder and ovarian cancer repeatedly rank serous ovarian cancer as the most likely type of cancer that may result among talc users. Dr. Cramer confirmed that in his testimony; "...invasive serous cancer, [is] the type most commonly associated with talc use." (Testimony of 8/8/16; see P320, L19) Neither Plaintiff was diagnosed with this condition. *Why was there no testimony presented to address this obvious incongruity?*
2. Talc was purportedly found in tissue surgically removed from each of the Plaintiffs. It was argued by Plaintiffs and their experts that inflammation is the root cause of all cancers. Yet there is nothing in the records nor expert reports demonstrating that the tissue samples were inflamed. *Why was there no testimony presented to address this obvious question?*
3. Positing Plaintiffs' contention that talc particles travel naturally through the female anatomy, from the perineum to the ovaries, then, *a fortiori*, the potential for talc particles to lodge elsewhere along the reproductive tract and create similar conditions would be apparent. Yet the only portion of the reproductive tract in which talc has purportedly caused cancer is the ovaries. Nothing was presented showing an increase in the other gynecologic cancers such as vaginal cancer, cervical cancer, uterine cancer, or fallopian tube cancer, which is what one would reasonably expect. *Why was there no testimony presented to address this obvious conundrum?*

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Summary of Dr. Chodosh's Testimony

As part of its preliminary overview of the expert testimony presented, the court is compelled to highlight the testimony of one witness in particular. Dr. Chodosh's testimony for Defendants was akin turning on the lights in a dark room. The failure of Plaintiffs' experts to articulate a plausible hypothesis for the biological mechanism by which talc purportedly causes ovarian cancer is a serious deficiency. After hearing Dr. Chodosh's testimony, it is apparent to the court that there was no articulation of a plausible hypothesis because it is unlikely that one can be made. Dr. Chodosh's testimony illustrates the huge hole in Plaintiffs' scientific methodology, namely, the failure to consider the biology of cancer. Dr. Chodosh's testimony and the scientific studies (see Appendix D) upon which he relies in formulating his opinions appear to support a reasonable hypothesis that talc does not cause cancer because it cannot cause cancer.

What follows are the most significant conclusions from Dr. Chodosh's testimony, none of which were addressed by anything Plaintiffs' experts presented, nor diminished in their impact on cross-examination.

1. Talc is *inert*. "...talc does not change gene expression in ovarian cells. Treating ovarian cells with talc didn't change the expression." (Testimony of 8/19/16; see P71, L2 thru P77, L13).
2. Talc is an anti-cancer property because it inhibits the formation of blood cells, and it cannot cause mutations.

> Q What do they show just in some --
>
> A In a thumbnail, it basically shows that talc actually inhibits the formation of blood vessel growth.
>
> Q Which is an anticancer property of talc?
>
> A Yes, that would be an anticancer property.

(See generally the testimony of 8/19/16; see P33, L23 thru P34, L7 and P39, L10 thru P53, L8).

See also the study by N. Najmunnis, et al., *Talc mediates angiostasis in malignant pleural effusions via endostatin induction* at Appendix D wherein these scientists concluded: "In conclusion, talc alters the angiogenic balance in the pleural space from a biologically active and angiogenic environmental to an angiostatis milieu. Functional improvement following

talc poudrage in patients with malignant pleural effusions may, in part, reflect these alterations in the pleural space."

3. Talc induces cancer cells to apoptosis but not to normal cells. (Testimony of 8/19/16; see P41, L5 thru P45, L3 and P143, L18 thru P145, L7).
4. It's universally accepted that mutations in critical genes is the mechanism that causes cancer, and talc doesn't cause mutations. (Testimony of 8/19/16; see P52, L22 thru P56, L9).
5. "Inflammation" is an extremely complex issue and it is unclear whether chronic inflammation is sufficient to induce cancer in the absence of a carcinogen. (Testimony of 8/19/16; see P177, L11 thru P181, L10).

VII. FOOD and DRUG ADMINISTRATION LETTER ON TALC

Much was made by counsel for both sides in their questioning of witnesses during the several days of the *Kemp* Hearing with regard to a letter from the Food and Drug Administration (FDA), dated April 1, 2014, hereinafter "the FDA letter." The FDA letter was in reply to the "Citizen Petitions" filed by Samuel S. Epstein, M.D., of the University of Illinois, School of Public Health, on behalf of the "Cancer Prevention Coalition." Said petitions (dated November 17, 1994 and May 13, 2008) requested the FDA to require all cosmetic talc products to bear a warning label. Particularly, with regard to talcum powder, the Coalition requested a prominent warning reading as follows: "Frequent talc application in the female genital area is responsible for major risks of ovarian cancer."

The court perused the FDA's letter on multiple occasions. Depending upon one's perspective, the letter can be cited for a great deal of importance, or, it might be said that the letter provides very little new information of significance to the issues that must be addressed herein. This court's reading falls into the latter category

There was limited discussion of the FDA's statutory and regulatory authority during the *Kemp* Hearing. Yet, there is a need to place the letter and the FDA's role into proper context. The pertinent regulation dealing with labeling of talcum powder or any other "cosmetic" product is set forth at Title 21 of the Federal Register. It states in pertinent part:

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§740.1 Establishment of warning statements.

(a) The label of a cosmetic product shall bear a warning statement whenever necessary or appropriate to prevent a health hazard that may be associated with the product.

(b) The Commissioner of Food and Drugs, either on his own initiative or on behalf of any interested person who has submitted a petition, may publish a proposal to establish or amend, under subpart B of this part, a regulation prescribing a warning for a cosmetic. Any such petition shall include an adequate factual basis to support the petition, shall be in the form set forth in part 10 of this chapter, and will be published for comment if it contains reasonable grounds for the proposed regulation.

Subpart "(a)" of Section 740.1 was discussed with one witness, and comments were made by counsel concerning the same. Yet there was no discussion by Plaintiffs' experts with regard to subpart "(b)." That subpart requires petitions such as those filed by Dr. Epstein and the Cancer Prevention Coalition to *include an adequate factual basis to support the petition.* Subpart "(b)" states that upon submission of an "adequate factual basis," the Commissioner of the FDA "either on his own initiative or on behalf of any interested person who has submitted a petition" has the authority to "publish a proposal to establish" a warning label for a "cosmetic product." That would include talcum powder. As noted by Deputy Director Steven M. Musser, Ph.D., the petitions were denied because they lacked sufficient "evidence of a causal association between talc use in the perineal area and ovarian cancer." In denying the petitions, the "FDA found" and articulated six points which the agency concluded were supported by its review of "an expanded literature search."

Relevant to the court's analysis are findings #2 and #4 of the FDA letter. Finding #2 expressed concerns with biases in the design of studies and uncontrolled confounding. It also noted that "no single study has considered all the factors that potentially contribute to ovarian cancer". Finding #4 states in relevant part, "[a] cogent biological mechanism by which talc might lead to ovarian cancer is lacking…" Nothing was presented by Plaintiffs' expert with regard to these two critical findings of the FDA.

The FDA letter is essentially an acknowledgement of the status quo, based upon its own "expanded literature search." In short, the real rationale that can be drawn from the FDA letter is that if there existed sufficient evidence linking talc causally to ovarian cancer, *viz.*, *an adequate*

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factual basis to support such a postulation, the FDA has the resources and regulatory authority to mandate a warning label for talcum powder.

VIII. DEFICIENCIES IN DR. COLDITZ'S METHODOLOGY

Dr. Graham Colditz is a brilliant scientist and a dazzling witness. His vocal inflection, cadence, and adroit use of histrionics are extremely effective. Dr. Colditz's reputation for his breadth of knowledge about cancer and the esteem in which he is held by his peers is well deserved. Yet, at times, it seemed that issues raised in these proceedings, and the questions posed to him, were a bit mundane for a scientist of his caliber.

At page 10 of his report of July 31, 2015, Dr. Colditz discusses "biologic plausibility." His discussion of the subject entails fewer than 75 words. He cites a total of four peer-reviewed articles in arriving at his opinion: "Thus it is established that talc can travel to the ovary, it causes an inflammatory response, and this mechanism is consistent with the increase of ovarian cancer that is observed."

Scrutiny of the articles cited in Appendix C does not support his conclusion. What follows is a brief discussion of the aforesaid learned treatises referenced by Dr. Colditz.

Roberta B. Ness: This paper is limited to a review of existent epidemiologic literature in the English language on the risk and protective factors for ovarian cancer and "proposes a novel hypothesis that a common mechanism underlying this disease is inflammation." Though talc exposure is mentioned, along with other theories of what may cause ovarian cancer, this paper does not discuss the means by which *talc can travel to the ovary*, nor does it discus the means by which talc causes *an inflammatory response* in the cells of the ovaries.

Jack Cuzik: This paper is limited to use of aspirin and NSAIDs for cancer prevention. This treatise does not discuss the means by which *talc can travel to the ovary*, nor does it discuss the means by which talc causes *an inflammatory response* in the cells of the ovaries.

Britton Talbert: This paper is limited to the "multiple lines of evidence" which "suggest that ovarian cancer may be related to chronic inflammation." In short, "this pooled analysis supports the hypothesis that regular aspirin use reduces ovarian cancer risk." This treatise does not discuss the means by which *talc can travel to the ovary*, nor does it discuss the means by which talc causes *an inflammatory response* in the cells of the ovaries.

Britton Talbert: This paper is limited to a discussion of the pro-inflammatory mechanisms that may explain "the increased risk linked to more lifetime ovulations, endometriosis, and exposure to talc and asbestos, as well as the decreased risk with non-steroidal anti-inflammatory drugs." This treatise does not discuss the means by which *talc can travel to the ovary*, nor does it the means by which talc causes *an inflammatory response* in the cells of the ovaries.

Even the most generous reading of these four cited articles reveals that none of them proffers an articulation of a hypothesis – nor a means by which to test the same – setting forth a biologic mechanism by which talc-based powder may/can/possibly does cause ovarian cancer. Dr. Colditz's reliance upon these four treatises supports a finding by this court that he has failed to make a systematic review of the scientific literature and has ignored the rudiments of the scientific method in arriving at his conclusion that, "[t]hus it is established that talc can travel to the ovary, it causes an inflammatory response, and this mechanism is consistent with the increase of ovarian cancer that is observed."

Further, with regard to "biologic plausibility," the court recalls Dr. Colditz's answer to the questions posed from the bench on this issue. Those questions dealt with a hypothesis on biologic causation postulated by Dr. Cramer. The exchange between the court and Dr. Colditz reads as follows:

> THE WITNESS: Yes, it is Dr. Cramer's study.
>
> THE COURT: Then turn to page 355. I'm determined to get an answer to this question. I asked it yesterday, and I wasn't able to get an answer. 355. Look at the second column. And then let's go to the last long sentence. "We have also proposed that talc use during periods of ovulation may carry greater risk, based upon the hypothesis that ovarian surface epithelial disruption and repair accompanying ovulation might allow talc to become entrapped within the inclusions cysts that form with ovulation." First question is, explain that to me in laymen's terms.
>
> THE WITNESS: Wow. Ovulation.

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THE COURT: A good scientist can do that. I'm sure you will. I understand ovulation.

THE WITNESS: You understand the ovulation. Right? That's -- and so he's saying that with ovulation and then in that disrupted epithelium, the presence of talc can more likely get --

THE COURT: How?

THE WITNESS: -- into a cell --

THE COURT: How? What's the cyst? What's an inclusion cyst?

THE WITNESS: Oh, so the -- this is the cyst that develops in an ovary that would have a talc particle in it as an inclusion cyst. So he's saying that with sort of the surface of the ovary has to repair each time it pops. And so there's --

THE COURT: That's a traumatic experience for that part of the body.

THE WITNESS: Yeah, right. And so there's inflammatory response.

THE COURT: Go ahead.

THE WITNESS: And so you got some macrophages and other things working to clean up and repair the epithelium. And if you've got the talc present at that time --

THE COURT: If you have it present at that time.

THE WITNESS: -- if you've ovulated, you've got higher likelihood is, I think, what he's trying to say.

THE COURT: And based upon your readings in preparation for your report, did you find any other peer-reviewed articles where Dr. Cramer discussed this hypothesis? And coupled with that, has anybody else discussed this hypothesis? Because if they do, I want to read it.

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THE WITNESS: So obviously others have discussed the description of talc in ovary. The IARC and others describe inflammation and the carcinogenic process.

THE COURT: I've heard lots of testimony. But I'm talking about this hypothesis.

THE WITNESS: This actual --

THE COURT: I'm not asking you to defend this hypothesis.

THE WITNESS: No, no.

THE COURT: I'm asking you to tell me has anybody else discussed it so I can read it.

THE WITNESS: I can't think of this specific mechanism for getting in -- being described.

THE COURT: So you don't know of any other study where Dr. Cramer did or anybody else did?

THE WITNESS: To look at the inclusion cysts?

THE COURT: That's what it says.

THE WITNESS: No.

THE COURT: Okay. Then I still don't have an answer to my question.

THE WITNESS: Then you don't. It's a great question.

THE COURT: It doesn't mean it's a good question. It just means I don't have an answer to it.

THE WITNESS: This is why there's got to be continuing studies to understand this whole process better.

(Testimony of 8/16/16, P312, L13 thru P315, L19).

To summarize this court's understanding of Plaintiffs' inability to explain the biological mechanism for how talc causes cancer, Dr. Colditz noted candidly, "This is why there's got to be continuing studies to understand this whole process better."

Though there are additional deviations from the scientific method included in Dr. Colditz's report – namely, the manner in which he blithely passes over most of the Hill criteria – the most egregious may be his failure/refusal to discuss *strength* of association, and how the same supports

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general causation. Repeated use of the term "significant" with regard to the R/R adds something to the discussion, but not much. As noted above, this court cannot be inflexibly bound by a R/R of "2.0" nor are the Hill criteria. A review of Dr. Colditz's testimony – both on direct and cross-examination – fails to establish a single instance in which he states that any number less than "2.0" for the R/R equates to sufficient strength to find a causal relation. His testimony supports neither general nor specific causation, nor does it address the question of where or whether a "significant" relationship becomes "causal."

Finally, Dr. Colditz's expert opinion is *ipse dixit* and has all the earmarks of a made-for-litigation presentation. We need look no further than his own past writings. *First,* in 2000 in his peer-reviewed article entitled, "Prospective Study of Talc and Ovarian Cancer," he concluded, "[o]ur results provide little support for any substantial association between perineal talc use and ovarian cancer risk overall..." *Second,* in his "2004 Handbook of Cancer Risk Assessment and Prevention," he lists talc as a "factor under study" in lieu of a modifiable factor which increases the risk of ovarian cancer. *Third,* as of 2011, on the website of the Alvin J. Siteman Cancer Center of which he is the Associate Director, the consensus of the Siteman scientific panel – which included both Dr. Colditz and Dr. Cramer – concluded that it was not appropriate to list talc as a risk factor on the "Your Disease Risk" portion of the website.

There is no challenge to Dr. Colditz's qualifications, nor that his testimony is relevant. Yet from the court's perspective, there are significant gaps in his methodology and analysis. He has committed the very error which Hill warned scientists against, namely, that the results of their research "...does not confer upon us a freedom to ignore the knowledge we already have." Dr. Colditz has overlooked the knowledge to be learned from laboratory research regarding the biology of cancer.

Applying the standards established in *Rubanick, supra,* 125 *N.J.* at 449, and *Landrigan, supra,* 127 *N.J.* at 420-1, the court concludes that the significant deficiencies in Dr. Colditz's methodology and analysis herein described, render his opinions inadmissible in these proceedings, and that the Defendants' motion to bar the testimony of Dr. Colditz is hereby GRANTED.

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IX. DEFICIENCIES IN DR. CRAMER'S METHODOLOGY

Dr. Cramer is a distinguished professional. His commitment to medical science generally, and to learning more about the potential health consequences to women from the frequent use of talcum powder in particular, have been unswerving throughout his career. Few people possess the knowledge he has acquired from case-control studies regarding the potential effects of talc *vis a vis* ovarian cancer. His passion for this subject is palpable and exemplary.

Dr. Cramer's study of this subject together with his examination and his analysis of the results of many case-control studies addressing the relationship between talc and ovarian cancer date back more than 30 years. In July, 1982 he published his initial peer-reviewed article on this subject entitled, "Ovarian Cancer and Talc: A Case-control Study." Over the past 34 years, Dr. Cramer has authored and co-authored numerous peer-reviewed articles on talc. He has also conducted several meta-analyses of other epidemiology reports. All those studies appear to demonstrate a consistent, albeit uniformly weak, association between talc and ovarian cancer.

Dr. Cramer is highly qualified and his testimony is relevant. Yet from the court's perspective, there is a large gap in his methodology. Dr. Cramer has totally ignored laboratory research regarding the biology of cancer and the ameliorative effects of talc on cancer. He has made the error that Hill expressly warned scientists against, *viz.*, that the results of their research "...does not confer upon us a freedom to ignore the knowledge we already have."

As discussed above, the research and existing studies cited in the testimony of Dr. Chodosh dismantled the premise of Dr. Cramer's opinions on the causal association between talc-based products and ovarian cancer. Dr. Cramer's failure to address the opinions of Dr. Chodosh and the results of laboratory research on the ameliorative effects of talc on cancer highlights the serious flaws in his methodology.

For purposes of this *Kemp* Hearing, the court must consider whether Dr. Cramer's testimony is sufficiently reliable to be presented to a jury. Defendants attack his opinions on both *general* and *specific* causation.

On the issue of *general causation*, Defendants attack the odds ratios (O/R) established in his report. Dr. Cramer notes that in general, his research – relying almost entirely upon case-control studies - confirms that there is an O/R of 1.29 between perineal talc use and ovarian cancer. As indicated in his report, Dr. Cramer performed a case-control study to generate his final conclusions.

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In both his report and in his testimony, Dr. Cramer opines that the causal association between ovarian cancer and the use of talc has been "significant" and consistent for 30 years. The O/R of 1.29 reported by Dr. Cramer is admittedly "weak" and neither he nor any other witness explained when/how a "significant" association becomes causal?

A retrospective case-control study is commonplace in the field of epidemiology, but as noted by the *Reference Manual* at page 576 such studies are considered less reliable than a prospective cohort study. Yet, that is almost entirely where Dr. Cramer devotes his research. According to Dr. Cramer, there have been 19 peer-reviewed scientific articles addressing the talc and ovarian cancer association since 1982. More recently there have been three very large cohort studies whose number of participants dwarfs those of the case-controls studies. (See Appendix A). Undermining the reliability of his testimony, Dr. Cramer is rigidly dismissive of the knowledge to be gained from the much larger cohort studies. On cross-examination, when asked if he had performed a meta-analysis of the three large cohort studies, he tartly replied, "I have not done that. The defense is very capable of doing that themselves." (Testimony of 8/8/16; see P324, L1 thru L8. See also his testimony at P199, L24 thru P200, L5).

Most troubling to the court is the effort made by Dr. Cramer to use epidemiology to prove *specific* causation. As noted by the *Federal Manual* at page 553, trial judges are warned of the overreliance upon such studies, "[a] final caveat is that employing the results of group-based studies of risk to make a causal determination for an individual plaintiff is beyond the limits of epidemiology." And again, the *Federal Manual* cautions, "[e]pidemiology is concerned with the incidence of disease in populations, and epidemiologic studies do not address the question of the cause of an individual's disease. This question, often referred to as specific causation, is beyond the domain of the science of epidemiology." (p. 608). In short, Dr. Cramer's methodology appears to be litigation driven rather than objectively and scientifically grounded.

The court uses the phrase *made-for-litigation* methodology for a reason. In all his prior peer-reviewed articles, Dr. Cramer never once stated that he believes talc causes ovarian cancer; not in his articles of 1982, 1999, 2000 (with Gertig) and 2007 does he make such an assertion. In fact, in his study of 2007, he concluded, "[w]e are not claiming that a causal relationship between ovarian cancer and talc is proven for this case or in general." Yet now, after having never made such a claim, he asserts here not only general causation, but specific causation as to both Plaintiffs,

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and purports to do so by re-analyzing old studies and subjectively mingling the various risk factors for each Plaintiff in order to prove ovarian cancer *by the numbers.* This "methodology" is not one based upon "prolonged, controlled, consistent and validated experiences". *Rubanick* at 436.

A final issue which must be addressed with regard to specific causation is the detailing of a hypothetical etiology of the disease in question and how the alleged substance is the malefactor. In his study of 1999 (See Appendix B), Dr. Cramer – in passing – made a partial articulation of a hypothesis for the biological mechanism by which talc purportedly causes ovarian cancer. That partial articulation is set forth in a single sentence which reads:

> We have also proposed that talc use during periods of ovulations may carry greater risk, based on the hypothesis that ovarian surface epithelial disruption and repair accompanying ovulation might allow talc to become entrapped within the inclusion cysts that form with ovulation. (p. 355).

This is the closest Dr. Cramer has ever come to postulating a hypothesis for the causal link between talc and ovarian cancer. He does not allude to this hypothesis in either the Carl or the Balderamma reports. Nor was he asked about this hypothesis by counsel on direct-examination.

Instead of a plausible explication of a hypothesis setting forth the biological mechanism of the causal link between talc-based powder and ovarian cancer, what the court received was a *made-for-litigation* methodology, to wit, the subjective mingling of risk factors to advance the base-line relative risk for each of the Plaintiffs (as members of the U.S. population) from 1.29 to 1.75 (Carl) and 1.79 (Balderamma). The knowledge learned to date from epidemiology studies involving talc and ovarian cancer is insufficient to prove ovarian cancer *by the numbers.*

Each of the Plaintiffs had significant risk factors for ovarian cancer to which Dr. Cramer's testimony showed a stark indifference. Ms. Carl had the following risk factors: obesity, nulliparity, infertility, past use of an IUD, psychotropic medication, smoking, and exposure to hair dye. Ms. Balderamma had the following risk factors: obesity, nulliparity, irregular cycles, early menarche (age 11), polycystic ovarian syndrome, past use of an IUD, and a potential BRCA gene diagnosis.

Despite his failure to eliminate – or make an objective accounting of – those multiple risks, Dr. Cramer leaps to specific causation *by the numbers.* He is not concerned that he hasn't even attempted to postulate a plausible biological hypothesis for how talc causes ovarian cancer as urged by factor #6 of the Hill criteria. His opinions rely upon an incomplete/irregular methodology

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unlike anything upon which his peers would rely, and appear to be grounded only in his instincts and personal predilections. In short, the mingling of various risk factors and the purported "synergy" between talc and other health conditions is highly speculative and does not conform to any methodology utilized in the scientific community.

Finally, Dr. Cramer and Plaintiffs' counsel would be better served to heed the wisdom contained in the FDA Letter of April 1, 2014. Finding #4 of "Epidemiology and Etiology Findings" reads in pertinent part: "A cogent biological mechanism by which talc might lead to ovarian cancer is lacking..." Hill criterion #6, to wit, **plausibility** (*i.e.*, whether there exists a biologically plausible *mechanism* by which the agent *could* cause the disease?) requires Plaintiffs' experts to articulate and support/defend a plausible *mechanism* by which talc *could* cause ovarian cancer. Their failure to do so is decisive in the court's analysis.

Applying the standards established in *Rubanick, supra,* 125 *N.J.* at 449, and *Landrigan, supra,* 127 *N.J.* at 420-1, the court concludes that the significant deficiencies in Dr. Cramer's methodology and analysis herein described, render his opinions inadmissible in these proceedings, and that the Defendants' motion to bar the testimony of Dr. Cramer is hereby GRANTED

X. RULING

As is true of most adversarial proceedings, the written reports and testimony of Plaintiffs' experts are much like a patch-work quilt; individual pieces that when sewn together create a single blanket. If well sewn, the blanket covers the issues required to meet Plaintiffs' burden of proof. Positing, for the sake of discussion, that each piece of cloth is sound, the fragments cannot become a quilt without thread. Without a clearly stated, demonstrable hypothesis of specific causation, grounded in a reliable methodology, there is no thread and the pieces of cloth remain disparate.

Accepting, for the sake of discussion, that the case-control studies relied upon by Dr. Cramer – to the exclusion of cohort studies, laboratory studies, cancer biology and the pronouncements of those agencies that study cancer – convey an inference that there is some type of causal association between talc and ovarian cancer, it means nothing without a hypothesis of specific causation. No witness for Plaintiffs ventured to articulate just how it is that talc in the ovaries, or, what it is about talc in the ovaries, that sets off a chain of events which purportedly causes ovarian cancer. Uttering the term inflammation does not explain the etiology of ovarian

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cancer, nor can the manipulation of numbers serve as a hypothesis for specific causation. Absent the thread, there is no quilt.

As the proponent of the evidence on general and specific causation, "the plaintiff bears the burden of establishing admissibility." *Kemp, supra,* 174 *N.J.* at 429. As discussed, the testimony of Plaintiffs' experts suffers from multiple deficiencies, the most salient of which are the narrowness and shallowness of their scientific inquiries and the evidence upon which they rely. Their peers in the scientific community would not rely upon such limited information.

Ultimately the admissibility of these experts' opinions depends "on the trial court's assessment of both [their] qualifications and [their] methodology." *Landrigan, supra,* 127 *N.J.* at 422. "The key to the admission of the opinion is the validity of the expert's reasoning and methodology." *Id.* at 414. Though both Plaintiffs' experts are eminently qualified, their areas of scientific inquiry, reasoning, and methodology are slanted away from objective science and towards advocacy. It is this court's conclusion that the opinions expressed by Plaintiffs' experts fail to demonstrate "that the data or information used were soundly and reliably generated and are of a type reasonably relied upon by comparable experts." *Rubanick, supra,* at 477.

For the reasons stated herein, the Defendants' motion to bar expert testimony and for entry of summary judgment as to both the Carl and Balderrama matters are hereby GRANTED.

With regard to the other expert witnesses of the Plaintiffs as well as Plaintiffs' cross-motions to bar the Defendants' experts, the Court will neither opine nor rule on the same. In light of the foregoing ruling, said petitions are of no practical significance and are deemed MOOT.

Nan C Johnson

NELSON C. JOHNSON, J.S.C.

Date of Decision: 9/2/16

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APPENDIX A

Cohort Studies

(1) Douching, Talc Use, and Risk of Ovarian Cancer

Gonzalez, Nicole, et al., *Epidemiology*, (The "Sister Study"), June 20, 2016.

Abstract

Background: Douching was recently reported to be associated with elevated levels of urinary metabolites of endocrine disrupting phthalates, but there is no literature on douching in relation to ovarian cancer. **Numerous case-control studies of genital talc use have reported an increased risk of ovarian cancer, but prospective cohort studies have not uniformly confirmed this association. Behavioral correlation between talc use and douching could produce confounding.**

Methods: The Sister Study (2003-2009) enrolled and followed **50,884 women** in the US and Puerto Rico who had a sister diagnosed with breast cancer. At baseline participants were asked about douching and talc use during the previous 12 months. During follow-up (median of 6.6 years) 154 participants reported a diagnosis of ovarian cancer. We computed adjusted hazard ratios (HR) and 95% confidence intervals (CI) for ovarian cancer risk using the Cox proportional hazards model.

Results: **There was little association between baseline perineal talc use and subsequent ovarian cancer** (HR: 0.73 CI: 0.44, 1.2). Douching was more common among talc users (OR: 2.1 CI: 2.0, 2.3), and douching at baseline was associated with increased subsequent risk of ovarian cancer (HR: 1.8 CI: 1.2, 2.8).

Conclusions: Douching but not talc use was associated with increased risk of ovarian cancer in the Sister Study.

Discussion

... with the exception of the finding that talc use was positively associated with serous ovarian cancer in the Nurses' Health Study, the prospective studies have not provided evidence supporting an association between talc use and ovarian cancer overall or between talc use and ovarian cancer overall among post-menopausal women.

... Because Sister Study participants all have a first-degree family history of breast cancer, they are more likely than the general population to develop ovarian cancer ... by design, we excluded women with a previous history of breast cancer ....

Our review of the literature suggests that our study is the first to examine the association between douching and ovarian cancer.

(2) **Perineal Powder Use and Risk of Ovarian Cancer** (The "Women's Health Initiative")

Houghton, Serena C., et al., *J Natl Cancer Inst, Oxford Journals*, (2014).

Background: Case-control studies have reported an increased risk of ovarian cancer among talc users; however, the only cohort study to date found no association except for an increase in serous invasive ovarian cancers. **The purpose of this analysis was to assess perineal powder use and risk of ovarian cancer prospectively in the Women's Health Initiative Observational Study cohort.**

Methods: Perineal powder use was assessed at baseline by self-report regarding application to genitals, sanitary napkins, or diaphragms and duration of use. The primary outcome was self-reported ovarian cancer centrally adjudicated by physicians.

Results: Among **61,576 postmenopausal women**, followed for a mean of 12.4 years without a history of cancer or bilateral oophorectomy, 52.6% reported ever using perineal powder. Ever use of perineal powder (hazard ratio $[HR]_{adj}$ = 1.06, 95% confidence interval [CI] = 0.87 to 1.28) was not associated with risk of ovarian cancer compared with never use. **Individually, ever use of powder on the genitals (HR_{adj} = 1.12, 95% CI = 0.92 to 1.36), sanitary napkins (HR_{adj} = 0.95, 95% CI = 0.76 to 1.20), or diaphragms (HR_{adj} = 0.92, 95% CI = 0.68 to 1.23) was not associated with risk of ovarian cancer compared with never use, nor were there associations with increasing durations of use.**

Conclusion: Based on our results, perineal powder use does not appear to influence ovarian cancer risk.

(3) **Prospective Study of Talc Use and Ovarian Cancer** (The "Nurses' Health Study")

Gertig, Dorota M., et al., *Journal of the National Cancer Institute,* Vol. 92, No. 3, February 2, 2000.

Background: Perineal talc use has been associated with an increased risk of ovarian cancer in a number of case-control studies; however, this association remains controversial because of limited supporting biologic evidence and the potential for recall bias or selection bias in case-control studies. In this study, we conducted a prospective analysis of perineal talc use and the risk of ovarian cancer.

Methods: The Nurses' Health Study is a prospective study of 121,700 female registered nurses in the United States who were aged 30-55 years at enrollment in 1976. Talc use was ascertained in 1982 by use of a self-administered questionnaire: after exclusions, **78,630** women formed the cohort for analysis. ... **We observed no overall association with ever talc use and epithelial ovarian cancer (multivariate RR = 1.09; 95% CI = 0.86-1.37) and no increase in risk of ovarian cancer with increasing frequency of use. ....**

Conclusion: our results provide little support for any substantial association between perineal talc use and ovarian cancer risk overall; however, perineal talc use may modestly increase the risk of invasive serous ovarian cancer. …

Discussion: To our knowledge, this is the first prospective analysis of talc use and ovarian cancer, and it addresses some of the potential limitations of previous case-control studies. **Because we ascertained talc exposure prior to case diagnosis, the possibility for recall bias, which has been raised as a potential explanation for previous positive findings in case-control studies, is eliminated, and selection bias is reduced.** We controlled for known or suspected ovarian cancer risk factors in the analysis, such as parity, oral contraceptive use, tubal ligation history, and body mass index, reducing the potential for uncontrolled confounding.

- The number of participants in the three large prospective population-based cohort studies on the association of talc-based powder and ovarian cancer conducted since 2000 total **191,090.**

APPENDIX B

Case Control Studies and Meta Analyses

(1) **Ovarian Cancer and Talc – A Case-Control Study**

[Dr. Cramer's initial study]

Cramer, Daniel W., et al., *Cancer*, 50:372-376, July 15, 1982.

Opportunities for genital exposure to talc were assessed in **215 white females** with epithelial ovarian cancers and in **215 control women** from the general population matched by age, race, and residence. Ninety-two (42.8%) cases regularly used talc either as a dusting powder on the perineum or on sanitary napkins compared with 61 (28.4%) controls. Adjusted for parity and menopausal status, this difference yielded a relative risk of 1.92 ($P < 0.003$) for ovarian cancer associated with these practices. Women who had regularly engaged in both practices had an adjusted relative risk of 3.28 ($P < 0.001$) compared to women with neither exposure. **This provides some support for all association between talc and ovarian cancer hypothesized because of the similarity of ovarian cancer to mesotheliomas and the chemical relation of talc to asbestos, a known cause of mesotheliomas.** ... No significant differences were noted between cases and controls in these exposures, although the intensity of talc exposure from these sources was likely affected by variables not assessed in this study.

...

(2) **Perineal Exposure to Talc and Ovarian Cancer Risk**

Harlow, Bernard L., et al., *Obstetrics and Gynecology,* 80:19-26, 1992.

Objective: We sought to determine whether the use of talc in genital hygiene increases the risk for epithelial ovarian cancer.

Methods: We interviewed **235 white women** diagnosed with epithelial ovarian cancer between 1984-1987 at ten Boston metropolitan area hospitals and **239 population-based controls** of similar race, age, and residence.

Results: Overall, 49% of cases and 39% of controls reported exposure to talc, via direct application to the perineum or to undergarments, sanitary napkins, or diaphragms, which yielded a 1.5 odds ratio (OR) for ovarian cancer (95% confidence interval [CI] 1.0-2.1). Among women with perineal exposure to talc, the risk was significantly elevated in the subgroups of women who applied it: 1) directly as a body powder (OR 1.7, 95% CI 1.1-2.7), 2) on a daily basis (OR 1.6, 95% CI 1.0-2.7). The greatest ovarian cancer risk associated with perineal talc use was observed in the subgroup of women estimated to have made more than 10,000 applications during years when they were ovulating and had an intact genital tract (OR 2.8, 95% CI 1.4-5.4); however, this exposure was found in only 14% of the women with ovarian cancer.

Conclusions: These data support the concept that a life-time patters of perineal talc use may increase the risk for epithelial ovarian cancer but is unlikely to be the etiology for the majority of epithelial ovarian cancers.

(3) **Perineal Powder Exposure and the Risk of Ovarian Cancer**

Cook, Linda S., et al., *American Journal of Epidemiology* 145:459-65, 1997.

This case-control study evaluated the risk of epithelial ovarian cancer associated with genital exposure to various forms of powder application. Cases included all women aged 20-79 years in three counties of western Washington who were diagnosed with borderline or invasive ovarian cancer from 1986 through 1988; 64.3% of eligible cases were interviewed. A sample of similarly aged women who lived in these counties, identified by random digit dialing, served as controls. ...

The "cases" totaled **329 women**; the cohorts totaled **422 women. Relative risk calculated at "1.5."**

(4) **Genital Talc Exposure and Risk of Ovarian Cancer**

Cramer, Daniel W., et al., *Int. J. Cancer*, 81:351-356, May 5, 1999.

Epidemiologic studies have suggested an increased risk for ovarian cancer associated with the use of talcum powder in genital hygiene, but the biologic credibility of the association has been questioned. ... Cases were more likely than controls (45% vs. 36^) to have used talc as a body powder in some manner, and the excess was confined to patients who used talc on the perineum directly or as a dusting powder to underwear or sanitary napkins. ... Exposure prior to rather than after the first livebirth appeared to be more harmful, and the association was most apparent for women with invasive serous cancers and least apparent for those with mucinous tumors. We conclude that there is a significant association between the use of talc in genital hygiene and risk of epithelial ovarian cancer that, when viewed in perspective of published data on this association, warrants more formal public health warnings.

... The "cases" totaled **563 women**; the cohorts totaled **523 women**.

We have also proposed that talc use during periods of ovulations may carry greater risk, based on the hypothesis that ovarian surface epithelial disruption and repair accompanying ovulation might allow talc to become entrapped within the inclusion cysts that form with ovulation. [NOTE: This statement at page 355 is Dr. Cramer's postulation of a hypothesis. He neither re-stated nor explained this hypothesis at the *Kemp* Hearing.]

The adjusted odds ratios ranged from 0.31 to 2.21.

(5) **Perineal Talc Exposure and Subsequent Epithelial Ovarian Cancer: A Case-Control Study**

Wong, Cheung, et al., *Obstetrics & Gynecology*, 93:372-6, 1999.

Objective: To evaluate the role of talcum powder use as a risk factor for the development of epithelial ovarian cancer.

Methods: In a case-control study, **499 patients** with epithelial ovarian cancer were frequency matched for age at diagnosis (± 5 years) with a control population of **755 patients**. The odds ratio (OR) for the development of epithelial ovarian cancer was estimated using logistic regression analysis with adjustment for age at diagnosis, parity, oral contraceptive use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location, history of tubal ligation, and previous hysterectomy.

Results: Two hundred twenty-one of 462 patients (47.8%) in the study population and 311 of 693 patients (44.9%) in the control population had ever used talcum powder (OR 0.92; 95% confidence interval [CI] 0.24, 3.62). A significant association between duration of talc use and development of epithelial ovarian cancer was not demonstrable for 1-9 years (OR 0.9; 95% CI 0.6, 1.5), for 10-19 years (OR 1.4; 95% CI 0.9, 2.2) or for more than 20 years (OR 0.9; 95% CI 0.6, 1.2). To eliminate the possible confounding variable of surgery for the management of ovarian cancer, we omitted 135 patients in the study population who underwent hysterectomy within 5 years of the diagnosis of ovarian cancer. Within this subgroup of patients, tubal ligation or hysterectomy among talc users still failed to demonstrate an increased risk for the development of ovarian cancer (OR 0.9; 95% CI 0.4, 2.2).

Conclusion: A significant association between the use of talcum powder and the risk of developing epithelial ovarian cancer is not demonstrable, even with prolonged exposure.

Discussion

The current study fails to demonstrate an association between the use of perineal talcum powder and a significant increase in the risk of epithelial ovarian cancer. These findings are at variance with a meta-analytic report by Gross and Berg, which demonstrated a modest increase in the risk of epithelial ovarian cancer among patients who had ever used talc. **In an analysis of ten epidemiologic studies, Gross and Berg calculated an adjusted OR of 1.29 (95% CI 1.02, 1.63).**

(6) **Genital Powder Exposure and the Risk of Epithelial Ovarian Cancer**

Rosenblatt, Karin A., et al., *Cancer Causes Control*, 22:737-742, May 5, 2011.

Abstract

Background: We conducted a population-based, case-control study to examine the association between the use of genital powder and ovarian cancer risk, including measures of extent and timing of exposure. We also assessed the relationship of powder use with risk of disease subtypes according to histology and degree of malignancy.

Methods: Information was collected during in-person interviews with **812 women** and epithelial ovarian cancer diagnosed in western Washington State from 2002 to 2005 and **1,313 controls**. Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (Cis).

Results: Overall, the perineal use of powder after bathing was associated with a slightly increased ovarian cancer risk (OR = 1.27, 95% CI: 0.97-1.66), which was most evident among women with borderline tumors (OR = 1.55, 95% CI: 1.02-2.37). We noted no clear pattern of risk increase on the basis of the extent of use, assessed as years in which powder was used, or as lifetime number of applications for invasive or borderline tumors, or their histologic subtypes. ...

Conclusions: The International Agency for Research on Cancer has designated perineal exposure to talc (via the application of genital powders) as a possible carcinogen in women. **A modest association of ovarian cancer with this exposure was seen in our study and in some previous ones, but that association generally has not been consistent within or among studies. Therefore, no stronger adjective than "possible" appears warranted at this time.**

(7) **The Association Between Talc Use and Ovarian Cancer – A Retrospective Case-Control Study in Two US States**

Cramer, Daniel W., *Epidemiology*, 27:334-346, May, 2016.

Background: Multiple studies of ovarian cancer and genital talc use have led only to consensus about possible carcinogenicity. Seeking greater clarity, we examined this association in **2,041 cases** with epithelial ovarian cancer and **2,100 age-and –residence-matched controls**.

...

Results: Overall, genital talc use was associated with an OR (95% CI) of 1.33 (1.16, 1.52) with a trend for increasing risk by talc-years. Women who used talc were more likely to be older, heavier, asthma sufferers, and regular analgesic users – none of which was a confounder. Dose-responses were more apparent for premenopausal women, especially nonsmokers and those heavier or postmenopausal users of menopausal hormones (hormone therapy [HT]). ...

Conclusion: Risks for epithelial ovarian cancer from genital talc use vary by histologic subtype, menopausal status at diagnosis, HT use, weight, and smoking. These observations suggest that estrogen and/or prolactin may play a role via macrophage activity and inflammatory response to talc.

(8) **Perineal Talc Use and Ovarian Cancer Risk: A Case Study of Scientific Standards in Environmental Epidemiology** [Meta Analysis]

Huncharek, Michael, et al., *European Journal of Cancer Prevention*, 20:501-507, November 6, 2011.

A number of observational studies (largely case-control) conducted over the last two decades suggest an association between use of talc powders on the female perineum and increased risk of ovarian cancer. A subset of these reports shows a roughly 30-60% increased risk of ovarian cancer associated with perineal talc exposure. A number of researchers partly base their conclusions of an association on the '...chemical relationship between talc and asbestos', the latter substance being a known human carcinogen. ...

Summary

...

These conclusions are based on a number of statistical, methodological, and biological issues. First, contrary to the assertions of Epstein (2008), findings from the cited studies are not consistent from study to study, and also differ by study design. **Two meta-analyses by Huncharek, et al. (2003) and Langseth, et al. (2008)both show significant differences in summary ORs between population-based and hospital-based case-control studies, with the latter showing generally null results. The Nurses' Health Study, the one prospective study that examined this association, found no risk with talc dusting.** Formal statistical tests for heterogeneity in both analyses support this finding. This fact suggests the existence of bias, and standard approaches to meta-analysis indicate that the pooled OR, or in this case an OR of 1.30, is not valid in the presence of heterogeneity. Huncharek and Muscat (2007) suggest multiple possible sources of bias that could produce a spurious positive finding, including unaccounted for effects of cancer treatment and confounding by smoking.

...

There is no coherent biological explanation as to how talc could induce cancer of the ovary. The theories put forth to explain the statistical association between talc and ovarian cancer have changed over time with little underlying consistency. The long-standing claim that talc is chemically 'similar' to asbestos and is therefore a carcinogen is a misunderstanding of the chemical and physical properties of talc.

(9) **Perineal Use of Talc and Risk of Ovarian Cancer [Meta Analysis]**

Langseth, H., et al., *The Cancer Registry of Norway*, October 15, 2007.

Abstract

Ovarian cancer is one of the most common gynaecological neoplasms, especially in industrialised countries. The aetiology of the disease is not well understood, except that inherited mutations in the breast cancer genes BRCA-1 and BRCA-2 account for up to 10% of all cases, and child-bearing, oral contraceptive use and breast-feeding reduce the risk. Some environmental exposures, notably talc and asbestos, have been suspected as ovarian carcinogens.

...

The association between talc use in the perineal region and ovarian cancer was investigated in one cohort study, and 20 cases-control studies. In the cohort study, arguably the strongest study because of its partly prospective ascertainment of exposure, there was no association between cosmetic talc use and risk of all subtypes of ovarian cancer combined.

...

To summarise the evidence in favour of an association, a very large number of studies have found that women who used talc experienced excess risks of ovarian cancer; some results were statistically significant and some were not. There was some indication in the cohort study of an increase in serous tumours. The evidence of talc migrating to the ovaries lends credibility to such possible association. **The main epidemiological evidence against the association is the absence of clear exposure-response associations in most studies, as well as the absence of an overall excess risk in the cohort study.**

...

The current body of experimental and epidemiological evidence is insufficient to establish a causal association between perineal use of talc and ovarian cancer risk. Experimental research is needed to better characterize deposition, retention and clearance of talc to evaluate the ovarian carcinogenicity of talc.

(10) **Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9.859 Controls**

Terry, Kathryn L., et al., *Cancer Prev Res (Phila),* 6(8):811-821, August, 2013.

Abstract

Genital powder use has been associated with risk of epithelial ovarian cancer in some, but not all, epidemiologic investigations, possibly reflecting the carcinogenic effects of talc particles found in most of these products. Whether risk increases with number of genital-powder applications and for all histologic types of ovarian cancer also remains uncertain. Therefore, we estimated the association between self-reported genital powder use and epithelial ovarian cancer risk in eight population-based case-control studies. Individual data from each study was collected and harmonized. Lifetime number of genital-powder applications was estimated from duration and frequency of use. **Pooled odds ratios were calculated using conditional logistic regression matched on study and age and adjusted for potential confounders. Subtype-specific risks were estimated according to tumor behavior and histology. 8,525 cases and 9,859 controls were included in the analyses.** Genital powder use was associated with a modest increased risk of epithelial ovarian cancer (odds ratio 1.24, 95% confidence interval 1.15-1.33) relative to women who never used powder. Risk was elevated for invasive serous (1.2, 1.09-1.32), endometrioid (1.22, 1.04-1.43), and clear cell (1.24, 1.01-1.52) tumors, and for borderline serous tumors (1.46, 1.24-1.72). Among genital powder users, we observed no significant trend (p=0.17) in risk with increasing number of lifetime applications (assessed in quartiles). We noted no increase in risk

among women who only reported non-genital powder use. In summary, genital powder use is a modifiable exposure associated with small-to-moderate increases in risk of most histologic subtypes of epithelial ovarian cancer.

...

This pooled analyses of eight case-control studies suggests that genital powder use is associated with a modest 20-30% increase in risk of developing epithelial ovarian cancer, including serous, endometrioid, and clear cell tumors, but is less relevant to invasive mucinous tumors. Our findings are consistent with and extend the findings of three meta-analyses that have reported an increased risk of epithelial ovarian cancer with genital-powder use by including dose response and histology specific analyses.

...

NOTE: The two meta-analyses performed by Langseth and Terry work with the same 8 studies in performing their analyses. Langseth arrived at an overall Odds Ratio of 1.35 and Terry arrived at an Odds Ratio of 1.24. The participating cases and controls examined totaled **18,384**.

APPENDIX C

Biologic Basis/Inflammation Studies

These studies which were cited by Dr. Graham Colditz his report in support of his statement of "Biologic Plausibility." (The "link" to each article permits the reader to assess whether the same supports Dr. Colditz's conclusions).

(1) Possible Role of Ovarian Epithelial Inflammation in Ovarian Cancer

Ness, Roberta B., et al., *Journal of the National Cancer Institute*, 91: 1459-1467, September 1, 1999. [http://www.ncbi.nlm.nih.gov/pubmed/10469746]

Summary

Neither incessant ovulation nor gonadotropin stimulation of ovarian estrogen provides a completely satisfactory explanation for the genesis of ovarian cancer. We have reviewed the data suggesting that an additional mechanism that may underlie ovarian cancer is inflammation, with concomitant rapid DNA turnover and effective repair, oxidative stress, and elevation of bioactive substances. Incessant ovulation, a process that has been linked to ovarian cancer risk, is associated with inflammation at the level of both the epithelium and the follicle. Other factors that cause local pelvic inflammation may also increase risk. Finally, tubal ligation and hysterectomy, which diminish the potential that ovarian epithelium will be exposed to initiators of inflammation, reduce risk. **Further observational and experimental data will be needed to confirm the hypothesis that inflammation is a central biologic process in ovarian cancer risk.**

(2) Aspirin and Non-Steroidal Anti-Inflammatory Drugs for Cancer Prevention: An International Consensus Statement

Cuzik, Jack., et al., *Lancet Oncol,* 10:501-507, May, 2009.
[http://www.ncbi.nlm.nih.gov/pubmed/19410194]

The panel planned to produce a consensus statement on the use of aspirin and other NSAIDs for cancer prevention; however, it became clear that gaps in our understanding of appropriate dose, duration, and age of use, would not support a formal risk-benefit analysis. ... **A specific benefit of aspirin over other NSAIDs is a lowered risk of occlusive cardiovascular events.** ...

Because of uncertainties about the minimum dose and duration of aspirin treatment needed to decrease cancer incidence, and the mixed beneficial and adverse effects on the cardiovascular and other organ systems, the panel concluded that further clinical studies were needed to assess the risk-benefit provide of NSAIDs. ...

Conclusion

Only treatment with aspirin combines the benefit of protection against cardiovascular disease with the potential to reduce the risk of some types of cancer. Aspirin might eventually be useful for the primary prevention of some cancers in patients who already qualify for prophylactic antiplatelet therapy on the basis of cardiovascular criteria.

(3) **Aspirin, Nonaspirin Nonsteroidal Anti-Inflammatory Drug, and Acetaminophen Use and Risk of Invasive Epithelial Ovarian Cancer: A Pooled Analysis in the Ovarian Cancer Association Consortium**

Trabert, Britton, et al., *J Natl Cancer Inst*, 106(2): djt431, February 5, 2014. [http://jnci.oxfordjournals.org/content/106/2/djt431.abstract]

Multiple lines of evidence suggest that ovarian cancer may be related to chronic inflammation. In addition to inflammatory factors associated with increased ovarian cancer risk.

Recently, intervention trials have shown that regular aspirin use is associated with reduced risk of several malignancies. However, these trials were not powered for rare cancer endpoints, and none of the clinical trials to date have evaluated ovarian cancer separately. …

Our study provides estimates on the effect of aspirin on ovarian cancer risk that should be considered in risk-benefit analyses for preventive aspirin use. However, detailed questions about frequency, dose, and duration will need to be evaluated in future studies including pooled data from cohort studies. …

In summary, this pooled analysis supports the hypothesis that regular aspirin use reduces ovarian cancer risk. Specifically, we report a statistically significant decreased risk of ovarian cancer with daily use of aspirin. Further biological and pharmacological research is necessary to understand the mechanisms of ovarian cancer risk reduction by aspirin use.

(4) **Pre-Diagnostic Serum Levels of Inflammation Markers and Risk of Ovarian Cancer in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial**

Trabert, Britton, et al., *Gynecologic Oncology* 135:297-304, November 2, 2014. [http://www.ncbi.nlm.nih.gov/pubmed/25158036]

Abstract

Objective: Pro-inflammatory mechanisms may explain the increased ovarian cancer risk linked to more lifetime ovulations, endometriosis, and exposure to talc and asbestos, as well as decreased risk with non-steroidal anti-inflammatory drugs. Limited data are available to estimate ovarian cancer risk associated with levels of circulating inflammatory markers.

Methods: We conducted a nested case-control study within the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Pre-diagnostic serum levels of 46 inflammation-related biomarkers (11 with a priori hypotheses; 35 agnostic) were measured in 149 incident ovarian cancer cases and 149 matched controls. Odds ratios (ORs) and 95% confidence intervals (Cis) were calculated using conditional logistic regression and adjusted for identified covariates.

Conclusion: These results suggest that CRP, IL-1*a*, IL-8, and TNF-*a* are associated with increased risk of subsequently developing ovarian cancer.

Introduction

Epidemiologic evidence implicates chronic inflammation as a central mechanism in the pathogenesis of ovarian cancer, the most lethal gynecologic cancer among women in the United States. **Chronic inflammation can induce rapid cell division, increasing the possibility for replication error, ineffective DNA repair and subsequent mutation.** Ovarian cancer has been linked to several events and conditions which are related to inflammation and repair, including incessant ovulation, endometriosis, exposure to talc and asbestos, and in some studies pelvic inflammatory disease. ... Understanding the role of inflammation in ovarian cancer etiology is complicated by growing recognition that there are at least two main types of these tumors, which differ clinically and biologically. Increasing evidence suggests that some high-grade serous carcinomas, the most common and lethal subtype, arise from the fimbria of the fallopian tube rather than the ovarian surface epithelium. ...

To gain a better understanding of the etiologic role of inflammation markers in ovarian cancer development, we conducted a nested case-control study within the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. We used multiplelxed inflammatory maker panels to measure 46 inflammation-related markers, including several inflammation markers with existing evidence of associations with ovarian function or ovarian cancer risk.

NOTE: None of the peer-reviewed articles cited by Dr. Colditz in his expert report of July 31, 2015 discusses talcum powder, talc's relationship to ovarian cancer, nor a hypothesis of how talc triggers a biologic mechanism resulting in ovarian cancer.

APPENDIX D

Studies Concluding That Talc is Not a Carcinogen, as per the Testimony of Dr. Lewis Chodosh

(l) **Talc Induces Apoptosis in Human Malignant Mesothelioma Cells *In Vitro***

Nasreen, Najmunnisa, et al., *Am J Respir Crit Car Med*, 161:595-600, February, 2000.

Pleurodesis with talc is an accepted method for the treatment of symptomatic pleural effusions secondary to mesotheliomas. Patients with mesothelioma who have talc-induced pleurodesis have a lower morbidity than do those who do not have pleurodesis. **The mechanisms whereby talc mediated these effects were considered to be secondary to a decrease or absence of a pleural effusion. The possibility that talc may directly affect malignant cells was not considered. The present study was designed to evaluate if talc directly effects cell death of malignant mesothelioma cells (MMC) or normal pleural mesothelial cells (PMC). ... The present study has demonstrated that talc induces apoptosis in MMC without affecting normal mesothelial cells of the pleura.**

(2) **Selective Apoptosis of Lung Cancer Cells with Talc**

Lee, P., et al., *European Respiratory Journal*, 35:450-452.

... **A number of studies have demonstrated superior efficacy of talc over other sclerosing agents commonly used for the palliation of malignant pleural effusions, and talc is the preferred pleurodesis agent according to a survey of chest physicians**. Despite talc's wide clinical use, the exact mechanisms for its efficacy as well as its apoptotic effects on lung cancer in vitro have not been studied. The objectives of our study were to determine if talc caused apoptosis of lung cancer cells, and to compare talc against other commonly administered intrapleural sclerosing agents by extending the experiments to include bleomycin and doxycline.

Our preliminary the use of talc for malignant effusion as it selectively causes apoptosis of lung cancer cells, and spares normal mesothelium pivotal for inciting inflammatory process necessary for pleural fibrosis. Studies are underway to compare the in vitro results with In vivo response, as well as to assess the impact on patient survival.

(3) **Talc Mediates Angiostasis in Malignant Pleural Effusions *via* Endostatin Induction**

Najmunnisa, N., et al., *Eur Respir J*, 29:761-769, 2007.

Abstract

Talc remains the most effective sclerosing agent for pleurodesis. However, its mechanism of action in resolving pleural malignant disease remains unclear.

The present study evaluated the angiogenic balance in the pleural space in patients with malignant pleural effusions (MPE) following talc insufflation. ...

In conclusion, talc alters the angiogenic balance in the pleural space from a biologically active and angiogenic environment to an angiostatis milieu. Functional improvement following talc poudrage in patients with malignant pleural effusions may, in part, reflect these alterations in the pleural space.

(4) ***In Vitro*** **Response of Rat Pleural Mesothelial Cells to Talc Samples in Genotoxicity Assays (Sister Chromatid Exchanges and DNA Repair)**

Endo-Capron, S., et al., *Toxic. In Vitro*, 7:714, January, 1993.

Abstract

The genotoxicity of three samples of talc has been determined using in vitro cell systems previously developed for testing asbestos fibres. **The talc samples used consisted of particles of respirable size in order to test the effect of particles likely to be deposited in the lung.** Genotoxicity was tested in cultures of rat pleural mesothelial cells (RPMC) using genotoxicity assays for unscheduled DNA synthesis (UDS) and sister chromatid exchanges (SCEs). **The effects were compared with those obtained with negative controls (attapulgite and anatase) and positive controls (chrysotile and crocidolite asbestos). In contrast to asbestos, none of the talc samples, nor the negative controls, and induced enhancement of (JDS or SCEs in treated cultures in comparison with the untreated cultures.**

[NOTE: As testified to by Dr. Chodosh, these rodents were exposed for their entire lifetime to living in "clouds of talc for hours a day ...". Testimony of 8/19/16, P104, L23 thru P106, L8].

(5) **Pycnogenol® Reduces Talc-Induced Neoplastic Transformation in Human Ovarian Cell Cultures**

Buzzard, Amber R., et al., *Phytother. Res.*, 2:579-586 (2007).

Talc and poor diet have been suggested to increase the risk of developing ovarian cancer; which can be reduced by a diet rich in fruit and vegetables. Talc is ubiquitous despite concern about its safety, role as a possible carcinogen and known ability to cause irritation and inflammation. It was recently shown that Pycnogenol® (Pyc; a proprietary mixture of water-soluble bioflavonoids extracted from French maritime pine bark) was selectively toxic to established malignant ovarian germ cells. **This study investigated talc-induced carcinogenesis and Pyc-induced chemoprevention.** Normal human epithelial and granulosa ovarian cell lines and polymorphonuclear neutrophils (PMN) were treated with talc, or pretreated with Pyc then talc. Cell viability, reactive oxygen species (ROS) generation and neoplastic transformation by soft agar assay were measured. Talc increased proliferation, induced neoplastic transformation and increased ROS generation time-dependently in the ovarian cells and dose-dependently in the PMN. Pretreatment with Pyc inhibited the talc-induced increase in proliferation, decreased the number of transformed colonies and decreased the ORS generation in the ovarian cells. **The data suggest that talc may contribute to ovarian neoplastic transformation and Pyc reduced the talc-**

induced transformation. Taken together, Pyc may prove to be a potent chemopreventative agent against ovarian carcinogenesis. ...

Effect of Talc on ROS Generation in Normal Ovarian Cells

Talc caused an initial dose-dependent decrease in ROS generation (24 h) which increased with time in OSE2a cells. However, as time increased, ROS generation rebounded and increased compared with the values at 24 h.

(6) **Utilization of Gene Profiling and Proteomics to Determine Mineral Pathogenicity in a Human Mesothelial Cell Line (LP9/TERT-1)**

Hillegass, Jedd M., et al., *Journal of Toxicology and Environmental Health, Part A*, 73:423-436, 2010.

Identifying and understanding the early molecular events that underscore mineral pathogenicity using *in vitro* screening tests is imperative, especially given the large number of synthetic and natural fibers and particles being introduced into the environment. ... To verify that LP9/TERT-l cells were more sensitive than other cell types to asbestos, **human ovarian epithelial cells (IOSE) were also utilized in microarray studies. Upon assessing changes in gene expression via microarrays, principal component analysis (PCA) of these data was used to identify patterns of differential gene expression. PCA of microarray data confirmed that LP9/TERT-l cells were more responsive than IOSE cells to crocidolite asbestos or nonfibrous talc, and that crocidolite asbestos elicited greater responses in both cell types when compared to nonfibrous talc, $Ti0_2$, or glass beads.** ...

(7) **Long Term Sequelae After Talc Pleurodesis for Spontaneous Pneumothorax**

Viskum, K., et al., *Pneumologic*, 43:105-106, 1989.

Talc is a hydrated magnesiumsilicate ($Mg_3,Si_2O_{10}(OH)_2$) which was found widespread industrial and medical use, i. ex. Powder for surgical gloves, wound powder and it has been used to provoke pleurodesis for more than 50 years. The main indications for the latter use or recurrent effusion due to malignancy and recurrent pneumothorax.

Due to the harmful action of asbestos, which too is a magnesiumsilicate, there has been some anxiety, that similar effects could be provoked by talc. So far we have no confirmation of this suspicion. One reason could be that talc is not harmful, another that the observation time after pleurodesis was too short We also have to observe, that talc in some cases has been contaminated with asbestos. ...

Conclusion

Talc pleurodesis for spontaneous pneumothorax seems not within the present observation time to carry any risk for the development of mesothelioma. Only moderate changes were observed in the pleura and no serious damage has occurred in ventilatory function, as judged from spirometry. **Talc pleurodesis is highly effective in preventing relapses of pneumothorax also on long term basis**.

(8) **Long-Term Follow-Up of Thoracoscopic Talc Pleurodesis for Primary Spontaneous Pneumothorax**

Gyorik, S., et al., *Eur Respir J*, 29:757-760, April 4, 2007.

Abstract

The aim of the present study was to evaluate the long-term outcome of patients with primary spontaneous pneumothorax treated with talc pleurodesis.

A follow-up study was undertaken in all patients with primary spontaneous pneumothorax who underwent talc pleurodesis for prolonged air leak or recurrence using thoracoscopy.

In total, 112 patients underwent pleurodesis and follow-up data was obtained in 63 (56% patients: 45 patients were available for clinical follow-up, 14 for telephone follow-up and four were dead. The causes of death were unrelated to the pleurodesis. There were no episodes of acute respiratory failure following pleurodesis. A total of 56 (95%) out of the cohort of 59 patients had a successful pleurodesis. Surgical pleurectomy was required in three (5%) patients for persistent air leak. Median duration of follow-up after talc pleurodesis was 118 months. Long-term success was observed in 53 (95%) out of 56 patients. Recurrent pneumothorax was observed in three (5%) out of 56 patients. Patients with successful talc pleurodesis had a median forced vital capacity (FVC) of 102% and median total lung capacity of 99% at follow-up. Comparing smokers and nonsmokers, the forced expiratory volume in one second (FEV_1) was significantly lower in smokers and there was a tendency for FEV_1 /FVC ratio to be lower in smokers.

Talc pleurodesis in patients with primary spontaneous pneumothorax via thoracoscopy is an effective procedure associated with normal lung function in patients who do not smoke.

(9) **Is Talc Pleurodesis Safe for Young Patients Following Primary Spontaneous Pneumothorax?**

Hunt, Ian, et al., *Interactive Cardio Vascular and Thoracic Surgery*, 6:117-120, 2007.

Summary

A best evidence topic in cardiothoracic surgery was written according to a structured protocol. **The question addressed was whether talc used for pleurodesis in young patients with a spontaneous pneumothorax has any long-term adverse effects.** One hundred and eighty-one papers were identified using the search below. Eight papers presented the best evidence to answer the clinical question. The author, journal, date and country of publication, patient group studies, study type, relevant outcomes, results, and study weaknesses of the papers are tabulated. **We conclude that talc pleurodesis in young patients with a spontaneous pneumothorax appears to have minimal long-term adverse consequences.**

APPENDIX E

Statements of Agencies Which Study Cancer

(1) **National Cancer Institute**

The NCI website was discussed repeatedly throughout the *Kemp* Hearing. Both sides acknowledge it to be an informative locus. The link below will take the reader to the NCI's most recent formal statement on talc and ovarian cancer; it is dated March 8, 2016 and is entitled, **Talc and ovarian cancer: what the most recent evidence shows.**

[http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=182.2437]

Ovarian cancer is rare. The incidence rate for ovarian cancer between 2006 and 2010 was 12.5 cases per 100,000 women. Women with a family history of ovarian cancer are at increased risk, and those with an inherited predisposition to ovarian cancer, such as a BRCA1 or BRCA2 mutation, have a very high risk of developing ovarian cancer (refer to the PDQ summary on *Genetics of Breast and Gynecologic Cancers* for more information). Other risk factors for ovarian cancer include obesity, nulliparity, and use of postmenopausal hormone therapy. Factors associated with a decreased risk of ovarian cancer include use of oral contraceptives, multiple pregnancies, breast-feeding, and tubal ligation.

The evidence is inadequate to determine whether perineal talc exposure is associated with an increased risk of ovarian cancer. Results from case-control and cohort studies are inconsistent. A meta-analysis of 16 studies observed an increased risk with the use of talc (RR, 1.33; 95% CI, 1.16-1.45); however, there was no evidence of a dose response. A pooled analysis from the Ovarian Cancer Association Consortium, composed of multiple case-control studies, included 8,525 cases and 9,859 controls. A modest increased risk of epithelial ovarian cancer associated with genital powder use (OR, 1.24; 95% CI, 1.15-1.33) was observed but the trend across increasing lifetime number of applications was not statistically significant (*P* trend = .17). Updated: February 4, 2016; Accessed: August 4, 2016. ...

(2) **U.S. Food and Drug Administration.** FDA Website accessed August 4, 2016

Protecting and Promoting *Your* Health.

Published scientific literature going back to the 1960s has suggested a possible association between the use of powders containing talc and the incidence of ovarian cancer. However, these studies have not conclusively demonstrated such a link, or if such a link existed, what risk factors might be involved. Nevertheless, questions about the potential contamination of talc with asbestos have been raised since the 19702.

See also the court's discussion of the FDA letter of 4/1/14 and of the CFR 740.1 (both at Section VII of this Opinion).

FDA Website accessed September 1, 2016.
[Code of Federal Regulations, Title 21, Volume 3, Revised as of April 1, 2015]
[CITE: 21CFR182.2437]

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER B--FOOD FOR HUMAN CONSUMPTION (CONTINUED)

PART 182 -- SUBSTANCES GENERALLY RECOGNIZED AS SAFE

Subpart C--Anticaking Agents

Sec. 182.2437 Magnesium silicate.

(a) Product. Magnesium silicate.

(b) Tolerance. 2 percent.

(c) Limitations, restrictions, or explanation. This substance is generally recognized as safe when used in table salt in accordance with good manufacturing practice.

[http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=182.2437]

(3) **American Cancer Society**

It has been suggested that talcum powder might cause cancer in the ovaries if the powder particles (applied to the genital area or on sanitary napkins, diaphragms, or condoms) were to travel through the vagina, uterus, and fallopian tubes to the ovary.

Many studies in women have looked at the possible link between talcum powder and cancer of the ovary. Findings have been mixed, with some studies reporting a slightly increased risk and some reporting no increase. Many case-control studies have found a small increase in risk. But these types of studies can be biased because they often rely on a person's memory of talc use many years earlier. Two prospective cohort studies, which would not have the same type of potential bias, have not found an increased risk.

For any individual woman, if there is an increased risk, the overall increase is likely to very be small. Still, talc is widely used in many products, so it is important to determine if the increased risk is real. Research in this area continues.

[http://www.cancer.org/cancer/cancercauses/othercarcinogens/athome/talcum-powder-and-cancer]

(4) **World Health Organization, International Agency Research on Cancer** (p. 412-413).

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of inhaled talc not containing asbestos or asbestiform fibres.

There is *limited evidence* in humans for the carcinogenicity of perineal use of talc-based body powder.

6.2 Cancer in experimental animals

There is *limited evidence* in experimental animals for the carcinogenicity of talc not containing asbestos or asbestiform fibres.

6.3 Overall evaluation

Perineal use of talc-based body powder is *possibly carcinogenic to humans (Group 2B).*

6.4 Rationale

In making this evaluation the Working Group considered the human and animal evidence as well as evidence regarding the potential mechanisms through which talc might cause cancer in humans. ... For perineal use of talc-based body powder, many case-control studies of ovarian cancer found a modest, but unusually consistent, excess in risk, although the impact of bias and potential confounding could not be ruled out. In addition, the evidence regarding exposure-response was inconsistent and the one cohort study did not provide support for an association between talc use and ovarian cancer. Concern was also expressed that exposure was defined in a variety of ways and that some substances called talc may have contained quartz and other potentially carcinogenic materials. A small number of Working Group members considered the evidence to be inadequate. Despite these reservations, the Working Group concluded that the epidemiological studies taken together provide *limited evidence* of an association between perineal use of talc-based body powder and an increased risk for ovarian cancer.

[NOTE: All italicized words in original text]

(5) **The American College of Obstetricians and Gynecologists**, Frequently Asked Questions FAQ096, Gynecologic Problems

What is cancer of the ovary?

Cancer of the ovary is a disease that affects [effects] one or both ***ovaries***.

What are the risk factors for epithelial ovarian cancer?

Certain risk factors are associated with epithelial ovarian cancer. The following factors have been shown to increase a woman's risk of getting cancer of the ovary:

- Age older than 55 years.
- Family history of breast cancer, ovarian cancer, colon cancer, or endometrial cancer (cancer of the lining of the ***uterus***)
- Personal history of breast cancer
- Certain changes (***mutations***) in ***BRCA1*** or ***BRCA2***
- Never having had children
- Infertility
- ***Endometriosis***

[NOTE: All bold words in original text]