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NELSON C. JOHNSON, J.S.C.

COURT INITIATED

IN RE: ACCUTANE LITIGATION

SUPERIOR COURT OF NEW JERSEY
LAW DIVISION: ATLANTIC COUNTY

CIVIL ACTION NO.: 271 (MCL)

ACCUTANE® MULTICOUNTY LITIGATION

ORDER

THIS MATTER having come before the Court on Defendant's Motion to bar expert testimony; and the court having conducted a plenary hearing on February 2, 3, 4, 5, 9, 10, 11 and 12, 2015, at which time the court heard from Russell Hewitt, Esquire, Paul W. Schmidt, Esquire, Colleen M. Hennessey, Esquire, and Andrew See, Esquire, on behalf of Defendant in support of their application; and Plaintiffs opposing this Motion, David R. Buchanan, Esquire, Paul G. Pennock, Esquire, MaryJane Bass, Esquire, and Timothy M. O'Brien, Esquire, appearing; and the court having received expert testimony and oral argument of counsel conducted pursuant the standards articulated by our Supreme Court in *Kemp vs. The State of New Jersey* 174 NJ 412 (2002), and for the reasons stated in the Memorandum of Decision of even date herewith; and for good cause shown;

IT IS ON THIS 20th DAY OF February, 2015, **ORDERED**:

1. Defendant's Motion to bar the testimony of Dr. Arthur Kornbluth and Dr. David Madigan is hereby GRANTED.

2. Defense counsel shall prepare a form of Order reciting those lawsuits effected by this ruling – including Captions and Docket Numbers - and submit the same to the Court on or before March 6, 2015. Said Order will not be entered until Plaintiffs' counsel have an opportunity to be heard on the form of the same, particularly the precise Captions and Docket Numbers.

Nelson C. Johnson

NELSON C. JOHNSON, JSC

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IN RE: ACCUTANE LITIGATION	**SUPERIOR COURT OF NEW JERSEY LAW DIVISION: ATLANTIC COUNTY** **CIVIL ACTION NO.: 271 (MCL)** **ACCUTANE® MULTICOUNTY LITIGATION**

OPINION

RE: KEMP HEARING ON BROAD ISSUE OF CROHN'S DISEASE

DECIDED: FEBRUARY 20, 2015

APPEARANCES: DAVID R. BUCHANAN, ESQUIRE, PLAINTIFF
PAUL G. PENNOCK, ESQUIRE, PLAINTIFF
MARYJANE BASS, ESQUIRE, PLAINTIFF
TIMOTHY M. O'BRIEN, ESQUIRE, PLAINTIFF

RUSSELL HEWITT, ESQUIRE, DEFENDANT
PAUL W. SCHMIDT, ESQUIRE, DEFENDANT
COLLEEN M. HENNESSEY, ESQUIRE, DEFENDANT
ANDREW SEE, ESQUIRE, DEFENDANT

NELSON C. JOHNSON, J.S.C.

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

I. POSTURE OF ISSUES BEFORE THE COURT

This matter is before the court on the Motion of the Defendants, Hoffman-LaRoche, Inc. and its related corporate entities, seeking relief against the Plaintiffs, all of whom brought claims alleging that a medication manufactured by the Defendant has caused them to develop Crohn's Disease.

The first lawsuit in the Accutane Litigation in the Superior Court of Atlantic County was filed on July 23, 2003. On May 2, 2005, pursuant to R. 4:38A, the New Jersey Supreme Court designated this litigation as a Multi-County Litigation (MCL), to receive centralized management by this court. Throughout the past 10(+) years, significant efforts by many professionals have been exerted to clarify the issues raised by Plaintiffs' claims. This court is confident that every avenue of legal and scientific research has been explored by capable legal counsel and learned scientists, and that the litigants' interests are well represented.

Presently before the court is a challenge brought by the Defendant to the Plaintiffs' contention that, among genetically pre-disposed persons, the ingestion of Accutane can be a proximate cause of Irritable Bowel Disease and, more particularly, the variant thereof known as Crohn's Disease. That challenge was heard, and expert testimony, together with oral argument of legal counsel, were received by the court at a plenary hearing conducted pursuant the standards articulated by our Supreme Court in *Kemp v. State of New Jersey* 174 *N.J.* 412 (2002), (hereinafter a "Kemp Hearing") as required by Evid. R. 104. The court conducted said hearing on February 2, 3, 4, 5, 9, 10, 11 and 12, 2015.

Defense counsel argues that based upon the most recent authoritative studies, there is no reliable scientific evidence to support Plaintiffs' contention, and that Plaintiffs' experts must therefore be barred from testifying at trial in support of that contention. In reply, Plaintiffs argue that their experts are qualified by education, training, and experience and that their opinions are 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 court's task may be stated as follows: *Query,* have the Plaintiffs shown that their experts' theories of causation are sufficiently reliable as being based on a sound, adequately-founded scientific methodology, to wit, relying upon methods upon which experts in their field would reasonably rely in forming their own (possibly different) opinions about what caused the Plaintiffs' disease?

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." See *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 hypothesis of causation advanced by Plaintiffs' experts is 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 all such reports, abstracts, peer-reviewed studies, etc. ("treatises" or "scientific literature") relied upon by the witnesses in formulating their opinions; said items total in excess of 400 treatises, most relating to Inflammatory Bowel Disease (IBD) and Crohn's Disease (CD). The court is grateful to counsel for these submissions; they were invaluable in preparing for the Kemp Hearing.

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 a valuable tool, providing excellent guidance in sifting through the information generated at the Kemp Hearing because it is indicative of what the scientific community deems to be reasonable. At this hearing, the court is asked to assess whether the experts in the field would reasonably rely on methods and data as Plaintiffs' experts have done. Through the *Reference Manual*, the scientific community speaks to trial courts and confirms what may be considered to be reasonable.

III. FINDINGS OF FACT

Based upon consideration of the submissions and arguments of counsel, the court's reading of the learned scientific treatises referenced herein, and a careful review of all witnesses' testimony, the court makes the following findings.

A. Expert Witnesses

The four witnesses who testified at the Kemp Hearing are exceptionally learned and accomplished professionals. Their credentials are impressive and each is a leader in his/her profession. The court benefited greatly from their opinions. A brief profile for each witness follows:

B. Witnesses for Plaintiffs

(1) Arthur A. Kornbluth, M.D.: Dr. Kornbluth is a distinguished physician and scientist. He is graduate of Brooklyn College and the Downstate Medical School, and serves as Clinical Professor of Medicine at the Icahn School of Medicine at Mount Sinai University in New York City. He is Board-Certified in Internal Medicine and in the subspecialty of Gastroenterology. He has received numerous awards ("Excellence in Teaching" multiple times) and has published extensively, including 100(+) peer-reviewed articles, abstracts and textbook chapters. He has served as editor and a peer-reviewer to multiple scientific journals.

(2) David Madigan, Ph. D.: Dr. Madigan is a Professor of Statistics at Columbia University and Executive Vice President of Arts & Sciences and Dean of the Faculty. He was educated at Trinity College in Dublin, Ireland and was formerly at Rutgers University where he served as Director of Institute of Biostatistics. He has published 150(+) technical papers in biostatistics, pharmacovigilance, etc. He has served as an investigator on a pilot project sponsored by the FDA for development of an active surveillance system for monitoring the safety of FDA-regulated medical products.

C. Witnesses for Defendant

(1) Steven N. Goodman, M.D., M.H.S. Ph. D.: Dr. Goodman is a distinguished scientist and physician who specializes in epidemiology. Educated at Harvard University, New York University, and Johns Hopkins University, he has A.B., M.D. and Ph. D. degrees. He has worked in several institutional settings and is currently at Stanford University where he is a Professor and Associate Dean for Clinical Research. He has devised standards and procedures for numerous epidemiological reports. He has worked as an editor on various publications and received numerous awards and academic certifications in his area of expertise.

(2) Maria Oliva-Hempker, M.D.: Dr. Oliva-Hempker is a Professor of Pediatric IBD and Chief of Division of Pediatric Gastroenterology & Nutrition at Johns Hopkins University School of Medicine. She has published 70(+) peer-reviewed treatises, book chapters in seven medical texts, and is Editor-in-Chief of *Your Child and Inflammatory Bowel Disease.* She regularly serves as a peer reviewer of treatises on IBD and is a member of the National Committee which prepares examinations for board certification by practicing gastroenterologists.

Dr. Oliva-Hempker has served on and chaired various gastroenterology committees, and maintains a visible profile educating the public on IBD.

D. Isotretinoin a/k/a Accutane. This case concerns Accutane's alleged propensity to cause IBD, particularly Crohn's Disease. Accutane was approved by the Food and Drug Administration ("FDA") in 1982 to treat recalcitrant nodular acne, a severe and disfiguring skin disease causing large cystic lesions on the face and back of those people affected. Chemically, Accutane is Isotretinoin, a type of retinoid, which is a derivative of Vitamin A.

Isotretinoin suppresses the production of oil and waxy material produced in the sebaceous glands. Dermatologists report that it is highly effective in treating nodular acne that has not responded to standard treatments. Isotretinoin is the only FDA approved medication for treating severe nodular cysts. Together with the warnings included on the label and packaging, Isotretinoin also has several other common/routine side effects, including dry skin, lips, and eyes.

E. Crohn's Disease. Crohn's Disease (CD) is characterized by chronic full thickness inflammation that can occur anywhere in the gastrointestinal tract, from the mouth to the anus, but in approximately 98% of all cases affects the small bowel and colon. Typical symptoms include abdominal pain, chronic diarrhea, gastrointestinal bleeding, associated extra-intestinal problems such as inflammatory arthritis, rashes, mouth ulcers and increased risk of colon cancer.

The court's readings of the treatises furnished by counsel failed to yield a single peer-reviewed study professing to explicate a precise biological mechanism for the development of CD and IBD. Nearly all the scientific literature refers to the cause of CD and IBD as "unknown."

IV. CASE LAW PERTINENT TO COURT'S ANALYSIS

New Jersey's courts recognize that litigants claiming that they were harmed by ingestion of a pharmaceutical 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)

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 (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 referred to this test as "methodology based," that is, if the methodology by which the expert reached a conclusion is sound, the conclusion may be introduced into evidence. *Id.* at 438-440.

Pursuant to *Rubanick,* the key to reliability is that the expert's opinion must be 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 experiences of scientific research." *Id.* at 446.

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 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, 125 *N.J.* at 453, 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.

Following *Rubanick,* in *Landrigan v. Celotex Corp.,* 127 *N.J.* 404 (1992), *Caterinicchio v. Pittsburgh Corning*, 127 *N.J.* 428 (1992), and *Dafler v. Raymark 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* involved the relationship of asbestos to colon cancer; *Dafler* 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,* 127 *N.J.* at 419.

The Supreme Court in *Landrigan* ruled that a trial judge must consider all the bases of and processes by which an expert reaches a conclusion, "includ[ing] an evaluation of the validity both of the studies on which he relied and on 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.

As this court understands *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." *Id.* 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 plaintiff's injuries," but that "toxic torts, however, do not readily lend themselves to proof that is so particularized." *Id.* at 415. Accordingly, plaintiffs in toxic tort cases "may be compelled to resort to more general evidence, such as that provided by epidemiological studies." *Ibid.* 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.

Concomitantly with our state's evolution of the standard for scientific proofs required of a plaintiff asserting harm as result of exposure to a toxic substance were changes occurring in the federal courts. In *Daubert v. Merrell Dow Pharms.* 509 *U.S.* 579 (1993) the U.S. Supreme Court stepped away from the long-standing "Frye Test" enunciated 70 years earlier in *Frye v. United States, supra*, wherein it was held that expert opinion based on a scientific technique is inadmissible unless the technique is "generally accepted" as reliable in the relevant scientific community. Consistent with *Daubert,* the federal courts now utilize a more "flexible" standard in ruling on the admissibility of scientific testimony applying the rule that a trial judge's focus is "...the scientific validity and thus the evidentiary relevance and reliability of the principles that underlie a proposed submission...solely on principles and methodology, not on the conclusions that they generate."(*Id.* at 595-596). Following *Daubert,* the U.S. Supreme Court issued two additional decisions on the admissibility of scientific evidence, namely *General Electric v. Joiner,* 522 *U.S.* 136 (1997) and *Kumho Tire v. Carmichael* 526 *U.S.* 137 (1999) In light of "*Daubert* Trilogy," there is a significant body of federal case law relevant to these proceedings.

Several years later, our Supreme Court briefly addressed the *Daubert* standard in *State v. Harvey*, 151 *N.J.* 117, 168-170 (1997), affirming that *Landrigan* and *Rubanick* had similarly relaxed the "general acceptance" standard in toxic tort cases. Nevertheless, the *Harvey* Court refused to apply anything less than the "general acceptance" standard to scientific evidence in criminal cases.

Five years after *Harvey,* in *Kemp ex rel. Wright v. State of New Jersey* 174 *N.J.* 412, 430-432 (2002), our 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 been confirmed by the scientific community yet 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. In the course of the Kemp Hearing, an expert must be able to identify the factual basis for his/her conclusion, explain his/her methodology, and demonstrate that both the factual basis and underlying methodology are scientifically reliable, even if such opinion is not generally accepted by his/her peers.

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,* 125 *N.J.* at 450, emphasis added. Thus, at a Kemp Hearing, Plaintiff's burden is to demonstrate that the methodology used is consistent with valid scientific principles accepted in the scientific and medical communities. In considering that burden and assessing the totality of the evidence as presented through the parties' proofs, this court abides by the observation of the Supreme Court that "[T]he trial court's review, therefore, is as broad as the breadth of the proffer and the challenges thereto that the parties present." *Hisenaj, supra,* 194 *N.J.* at 19-20.

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

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. REVIEW OF EXPERT TESTIMONY AND SCIENTIFIC LITERATURE

A. Testimony of Experts

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 are presented to a jury must be in accordance with the standards expressed by our Supreme Court and the information presented by counsel. The court had the opportunity to observe closely the four witnesses presented by the parties. Based upon a careful reading of the witnesses' written reports, and consideration of their testimony, and in light of the totality of the evidence presented, I make the following observations:

(1) Arthur A. Kornbluth, M.D.: Dr. Kornbluth has studied the association of Isotretinoin to CD, generally, for the past seven years and more intensively for the past four years as result of his involvement in the Accutane litigation. He was requested by Plaintiffs' counsel to render his "opinions on the question of whether Accutane can cause CD." In formulating his opinions he relied upon: (1) the pathogenesis of CD and the aberrant immune responses observed over the years with his many patients [currently 1,000+]: (2) pharmacology of Accutane and its metabolites as related to the development of CD; (3) reports & assessments of CD and other gastrointestinal problems of persons who have taken Accutane; (4) large clinical trials in patients with CD; and (5) the documents produced by Roche in pre-trial discovery.

In addition to his postulation of the potential mechanisms that may contribute to the development of CD and IBD as result of Isotretinoin, Dr. Kornbluth examined the two sets of epidemiological reports relied upon by the Defense. He opined that all of the Defendant's eight risk assessment reports were invalid and that only the "Sivaraman Study" was reliable. Of the 10 prodrome reports analyzed by the Defense, only the "Pimentel Study" was reliable. Dr. Kornbluth also expounded on his theory regarding the applicability of studies involving the medications Natalizumab and Vedolizumab.

(2) David Madigan, Ph. D.: Dr. Madigan offered no opinions on the issue of "general causation" because he was not retained to do so. As he states at paragraph 5 of his report of December 15, 2014, he was requested by Plaintiffs' counsel to "assess the statistical power of extant observational studies that consider the association between Isotretinoin and CD, taking into account the possibility that symptom onset may precede diagnosis of CD by some time (that is a prodrome)."

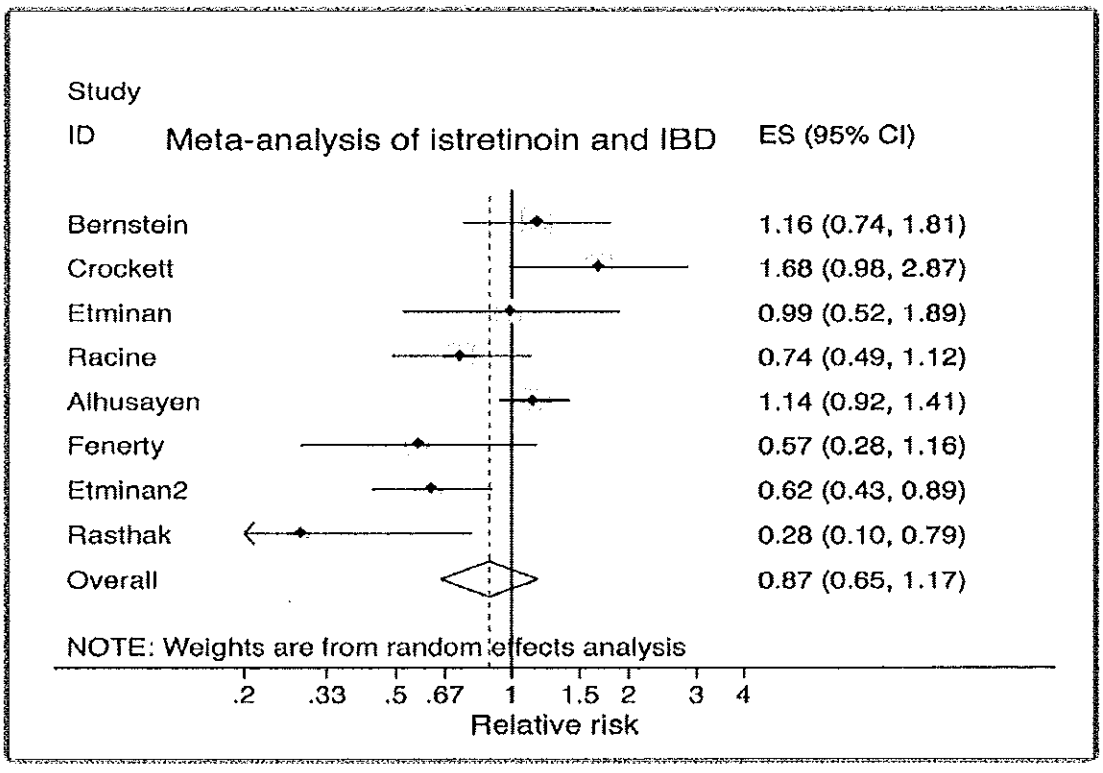
The entirety of Dr. Madigan's direct examination testimony was devoted to finding fault with those epidemiological studies relied upon by Defendant's counsel. Of the seven reports he analyzed, he found only one to be reliable, to wit, the abstract of a study done by Dr. Susil Sivaraman, et als. of the University of Nevada. Dr. Madigan disregarded the six epidemiological studies proffered by the Defense, because of failure to account for the prodrome of CD. He also disregarded the prodrome studies proffered by Defendants, relying instead upon the "Pimentel Study" discussed herein. Additionally, he opined that the meta-analysis conducted by Defendant's expert was inappropriate and misleading. In essence, Dr. Madigan is of the opinion that the epidemiological studies relied upon by the Defense "neither prove nor disprove" any causation of Isotretinoin and CD.

(3) Maria Oliva-Hempker, M.D.: Dr. Oliva-Hempker was requested by the Defense to provide an opinion as to whether there is a general causative link between Isotretinoin and CD, and to comment on the scientific reliability of the methodology employed by Dr. Kornbluth. In doing so, her testimony confirms that, generally, she examined the same data and treatises referenced by Dr. Kornbluth, but was critical of his methodology.

Dr. Oliva-Hempker opined that Plaintiffs' hypothesis of causality and biological mechanism are not plausible. She was critical of Dr. Kornbluth's reliance upon case reports, adverse event reports and animal studies. She also opined that his reliance upon a single epidemiological study comprised of a small number of subjects and his disregard of larger population-based studies as to both the risk estimates and the prodrome periods, was contrary to good science. Finally, she rejected the conclusions reached by Dr. Kornbluth with regard to studies involving Natalizumab and Vedolizumab.

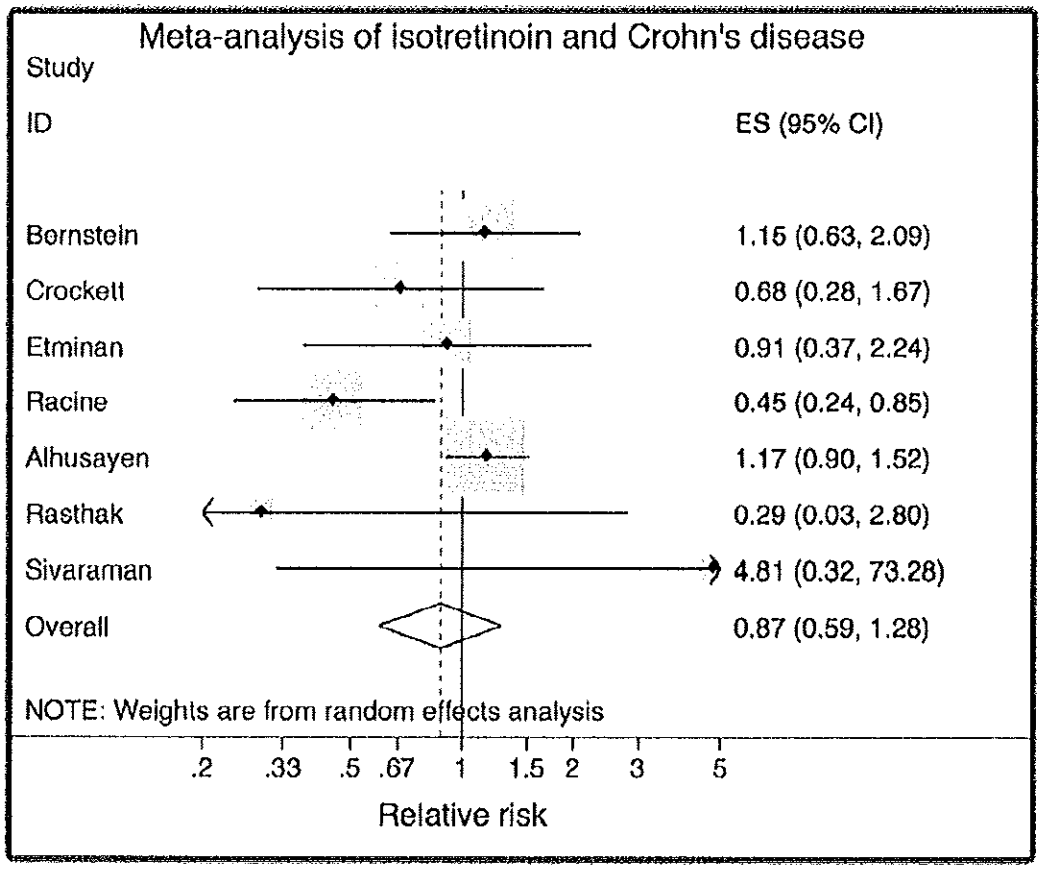
(4) Steven N. Goodman, M.D., M.H.S, Ph. D.: Dr. Goodman's report states that he was retained to provide his expert opinion as to the following issues: (1) is the scientific

methodology employed by Dr. Kornbluth and Dr. Madigan reliable?; and (2) is there a scientific basis for the Plaintiffs' claim that Isotretinoin is a cause of CD? In conducting his analysis of the opinions of the Plaintiffs' experts, Dr. Goodman reviewed a total of nine epidemiological studies and performed two meta-analyses which addressed the studies discussed at subpart "VI, D" as they relate to IBD. He conducted a meta-analysis of all the studies that examined the relationship between Isotretinoin and IBD and also a meta-analysis of all the studies that addressed Isotretinoin and CD specifically. He explained that Dr. Madigan and Dr. Kornbluth's disregard of the peer-reviewed articles on the prodrome for CD prevented a meta-analysis of those studies' results. He opined that "the strength of the meta-analysis is that no one feature, no one study, is determinant. You don't throw out evidence except when you absolutely have to." Dr. Goodman opined that Plaintiffs' failure to do a meta-analysis was critical because performing a meta-analysis "can get us closer to the truth." His two meta-analyses are as follows:



The Sivaraman Study is not included above because the authors did not report general IBD data. As discussed hereinafter, the Sivaraman Study is of very limited value.

The meta-analysis performed by Dr. Goodman on CD (including the Sivaraman Study) is as follows:



According to Dr. Goodman, the data produced by the eight studies (above and preceding graph) "rarely weigh against causality more heavily than this ... These results, combined with the lack of a known biologic mechanism for IBD causation, and a concomitant lack of a known biologic mechanism for Accutane causing the disease, makes this as strong a negative finding as can be found for most medications on environmental exposures." As shown, these studies tend to support an ameliorative effect of Isotretinoin.

Dr. Goodman also discussed the hierarchy of medical evidence and the weight/reliability accorded various types of scientific evidence and the distinction between hypothesis-generating evidence and hypothesis-testing evidence. He expressed strong opinions regarding the need for large population-based epidemiological studies, asserting that they have more weight with the research community.

B. Consensus in the Scientific Community. Based upon this court's readings of the treatises furnished by counsel, the only conclusion upon which everyone in the medical/scientific community seems to agree on is that Isotretinoin is the only medication that is effective in the treatment of severe recalcitrant nodular acne. The scientific literature furnished by counsel reveals that there is no consensus in the scientific community on whether or not Isotretinoin has a positive or a negative effect on consumers' physical well-being and general health, with the exception of acne. Additionally, with regard to consensus, there are no studies stating that Isotretinoin "causes" IBD. Such a statement would, of necessity, require an explication of a precise biological mechanism of the cause of IBD and no one has yet to venture more than alternate and speculative hypotheses on that question. Other than symptoms and risk factors, there appears to be little-to-no consensus in the medical/scientific community as to Isotretinoin's correlation to CD and IBD generally.

C. Acknowledgment of Risk Factors

This court agrees with the witnesses and counsel that "context" is always relevant. It is myopic to discuss the potential of a single medication as the cause of CD and IBD without a proper frame of reference. In addition to the role of the genes inherited from one's parents (the incidence of IBD among family members is a prominent risk factor), the treatises provided to the court recite an extensive list of factors commonly associated as "risks" for CD and IBD.

The risk factors referenced in the literature provided to the court by counsel cover a broad expanse and range from whether or not one has had an appendectomy, or was breast-fed as an infant, or suffers from stress or a Vitamin D deficiency, to the consumption of tobacco and alcohol products, refined sugars, meat and animal fats generally, fatty acids, fast food and, generally, whether or not one lives a "westernized life style."

In addition to these "environmental factors" there are four widely used FDA-approved medications (with hundreds of brands) which have a correlation to IBD, and which many

scientists and physicians (including the witnesses before the court) consider as risk factors for CD and IBD. Those medications are: (1) Aspirin - see S.S.M. Chang, M.D., "Aspirin in the etiology of Crohn's disease and ulcerative colitis: a European prospective cohort study" *Alimentary Pharmacology and Therapeutics,* July 2011; (2) NSAIDs or nonsteroidal anti-inflammatory drugs – see Joseph B. Felder, M.D. "Effects of Nonsteroidal Anti-inflammatory Drugs on Bowel Disease: A Case-Control Study" *American Journal of Gastroenterology,* August 2000; (3) Oral Contraceptives – see Dr. Hammed Khalil, "Oral contraceptives, reproductive factors and risk of inflammatory bowel disease." *GUT,* May 22, 2012; and (4) Antibiotics – see Anders Hviid, "Antibiotic use and inflammatory bowel diseases in childhood" *GUT,* October 21, 2010. As to antibiotics, the experts before the court acknowledge it as a risk factor.

Finally, providing the court with further "context" were two extensive review articles on risk factors. Those treatises are: Dr. Siew C. Ng, "Geographical variability and environmental risk factors in inflammatory bowel disease." *GUT,* January 18, 2013, and, Alexis Ponder and Millie D. Long, "A clinical review of recent findings in the epidemiology of inflammatory bowel disease." *Clinical Epidemiology,* 2013:5 237-247. These are comprehensive reviews. The S.C. Ng, et al. study reviews nearly 200 treatises; Ponder and Long nearly 100. The authors of these two review articles agree on many findings, but one in particular which concurs with the *Federal Manual*, namely, the need for large epidemiological studies to learn more about IBD.

S.C. Ng., et als. conclude in part, and recommend:

> Multicentre prospective cohort studies that follow large numbers of healthy individuals and at-risk first-degree relatives with high-risk genotypes to a new diagnosis of IBD are required to determine environmental risk factors.

Ponder and Long conclude in part, and recommend:

> As IBD is a relatively rare disorder, with complicated interactions between potential inciting agents, very large cohorts with detailed, prospectively collected, environmental exposure data will be needed.

Interestingly, after 30(+) years following FDA approval of Accutane, neither of these extensive studies even mentions Isotretinoin as a "risk factor."

D. Peer-Reviewed Scientific Treatises

In considering Isotretinoin's purported role in causing CD and IBD, the court believes that peer-reviewed scientific studies are relevant in evaluating expert testimony. The U.S. Supreme Court encouraged such consideration, stating "Another pertinent consideration is whether the theory or technique has been subjected to peer review and publication." *Daubert, supra,* 509 *U.S.* at 593.

As this court understands it, and as confirmed by Dr. Kornbluth, the peer review process is intended to maintain "academic rigor," reliability of findings and relevance in scholarly journals. The peer review process begins when a scientist prepares a written report on his/her study of a subject within his/her field of expertise. After composing the article and selecting a journal which publishes such reports, the author submits the article to an editor for review. Upon conclusion of his/her review, the editor then sends the scientific report to multiple scholars, who review the accuracy of the methodology utilized in arriving at the conclusions expressed in the report. Frequently, a reviewer challenges the author's opinion(s) and the author must then rebut and/or modify the effected portions prior to publication. Occasionally, a modified study, or no study, is published upon completion of the peer review process.

"Submission to the scrutiny of the scientific community is a component of 'good science,' in part because it increases the likelihood that substantive flaws in methodology will be detected." *Daubert, Ibid.*

That said, a peer-reviewed scientific treatise is not a *sine qua non.* As admonished by the *Federal Manual,* the peer review process is unlikely to catch "outright fraud" and "does not ensure that the work has been fully vetted in terms of the data analysis and proper application of research methods." (p.48) Nonetheless, Dr. Kornbluth is not a stranger to the peer review process. He has published 100(+) scientific treatises. In particular, in February, 2009, he published an article entitled "Ulcerative Colitis Practice Guidelines in Adults" in *The American Journal of Gastroenterology.* As revealed during his testimony at the Kemp Hearing, at the time when Dr. Kornbluth was preparing his peer-reviewed article, he declined the urgings of Dr. David Sachar to include comments referencing Isotretinoin as a cause of IBD, stating, "I feel strongly that we should delete the comment re Isotretinoin as a possible etiologic or exacerbating

cause." Now, before this court, he is prepared to say that Isotretinoin is a cause of IBD, yet to a more limited and less informed audience than his peer-reviewed article would have reached.

Dr. Kornbluth testified that his thinking has evolved since his exchange(s) with Dr. Sachar, still, he hasn't submitted his current hypothesis that Isotretinoin is a "cause" of CD, to the peer review process. "Expert opinions generated as the result of litigation have less credibility than opinions generated as the result of academic research or other forms of 'pure' research." *Soldo v. Sandoz Pharms. Corp.* 244 *F. Supp. 2d* 434, 527 (W.D. Pa. 2003). "The expert's motivation for his/her study and research is important. ... We may not ignore the fact that a scientist's normal work place is the lab or field, not the courtroom or the lawyer's office." *Id.* at 528.

One would reasonably anticipate that at this stage in his distinguished career as a scholar in the field of gastroenterology, Dr. Kornbluth would want to share the research supporting his hypothesis with the medical community so as to advance scientific knowledge, including his unprecedented inferences from the treatment effects of Natalizumab and Vedolizumab. Instead, he confines his audience to lay people in a court room. As stated by the court in *Perry v. United States,* 755 *F. 2d* 888, 892 (11th Cir. 1985) "The examination of a scientific study by a cadre of lawyers is not the same as its examination by others trained in the field of science or medicine."

[NOTE: On cross examination, Dr. Kornbluth conceded that there was nothing preventing him from writing a letter to the editor or other opinion piece formally criticizing the flaws which he believes are existent in both the risk assessment and prodrome studies. With regard to his ability to write a peer-reviewed article, counsel disputes whether or not Dr. Kornbluth is bound by the terms of the confidentiality agreement. That document was not presented to the court. The court is apprised of the fact that there is an extensive public record, where most – if not all – of the documents relied upon and referenced by Dr. Kornbluth, have been discussed in open court, the same occurring in prior litigation dating back to April 2, 2007.]

VI. ANALYSIS OF THE TOTALITY OF THE EVIDENCE PRESENTED.

A. Epidemiology Studies

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 studies as an alternate means of proving general causation. According to the *Reference Manual*, at p. 723-724, large epidemiological studies are some of the strongest medical/scientific evidence.

There are two types of epidemiological studies: (1) experimental studies, and (2) observational studies. Experimental studies, in the form of randomized clinical trials or true experiments, usually comprised of two groups: one exposed to the agent in question, and the other not exposed. In observational studies, individuals who have been exposed to the agent at issue are observed and compared to a group of individuals who've never been exposed to the agent.

The two primary types of observational studies are: (1) cohort studies, and (2) case-control studies. Cohort studies compare the incidence of disease among individuals exposed to an agent with an unexposed group; case-control studies look at the frequency of exposure among individuals who have the disease as compared to a group of individuals who do not have the disease. According to the *Reference Manual*, the consensus of the scientific community is that large population-based studies are more likely to produce meaningful information. Unsystematic clinical observations or case reports and adverse event reports are at the bottom of the evidence hierarchy.

The typical use of large population-based studies is in connection with "general causation." As noted in the the *Reference Manual.* (p. 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* (p. 552) cautions trial judges that "it should be emphasized that *an association is not equivalent to causation.*" (emphasis in the original text)

Additionally, as stated by the court in *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 *F. Supp. 2d* 584, 591, (D.N.J. 2002) in evaluating epidemiological studies, the court must be mindful of the fact 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.

As noted by the court in *Soldo, supra,* 244 *F. Supp. 2d* at 434, epidemiology studies are critical in proving cause and effect in a claim such as this.

> The very purpose of epidemiology is to serve the type of testing function required by *Daubert*, i.e., to discern accurately the effect of a particular agent on a disease against the background of the natural occurrence of the disease in the relevant population. Stated otherwise, epidemiology is the scientific methodology that allows testing of the hypothesis that substance A causes effect B.

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 over the past 10 (+) years on the possible association of Isotretinoin and IBD. As admonished by the *Reference Manual* (p. 576),

> [C]ommon 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.

This common sense precept is a valuable prism through which to begin the scrutiny of the validity of an epidemiological study and its value in informing the scientific community – as well a court - on a particular area of concern.

Those reports of epidemiology studies on which the court heard testimony and examined in assessing the plausibility of finding a causal connection between Isotretinoin and CD/IBD are:

1. Bernstein, C.N. et al., "Isotretinoin Is Not Associated With Inflammatory Bowel Disease: A Population-Based Case-Control Study." [*American Journal of Gastroenterology,* November, 2009.] The study comprises approximately 21,500 subjects.

2. Crockett, S.D. et al., "Isotretinoin Use and the Risk of Inflammatory Bowel Disease: A Case-Control Study." [*American Journal of Gastroenterology,* February 2010.] The study comprises approximately 29,000 subjects.

3. Alhusayen, R.O. et al., "Isotretinoin Use and the Risk of Inflammatory Bowel Disease: A Population-Based Cohort Study." [*The Society for Investigative Dermatology,* 2012.] The study comprises approximately 1,700,000 subjects.

4. Etminan, M. et al., "Isotretinoin and the Risk of Inflammatory Bowel Disease: A Retrospective Cohort Study." [JAMA DERMATOL, FEB 2013] The study comprises approximately 80,000 subjects.

5. Etminan, M. et al., "Isotretinoin and Risk for Inflammatory Bowel Disease: A Nested Case-Control Study and Meta-Analysis of Published and Unpublished Data. [JAMA DERMATOL February 2013, 149(2): 216-20.] The study comprises approximately 45,5000 subjects.

6. Fenerty, S. et al., "Impact of Acne Treatment on Inflammatory Bowel Disease." [See JAMA DERMATOL April, 2013] The study comprises approximately 175,000 subjects.

7. Racine A. et al., "Isotretinoin and the Risk of Inflammatory Bowel Disease: A French Nationwide Study." [See *The American Journal of Gastroenterology,* February 18, 2014.] The study comprises approximately 44,000 subjects.

8. Rashtak, S. et al., "Isotretinoin Exposure and the Risk of Inflammatory Bowel Disease." [See JAMA DERMATOL September 10, 2014] The study comprises approximately 1,000 subjects.

9. Sivaraman, S. et al., "Risk of Inflammatory Bowel Disease From Isotretinoin: A Case-Control Study." This is an abstract not reduced to a formal written report, comprising 1/4 page in the October, 2014, Edition of the *American Journal of Gastroenterology.* The study comprises a total of 509 subjects.

A list of the epidemiological studies compiled by Dr. Goodman and examining the relationship for Isotretinoin, IBD and Crohn's disease, together with a meta-analysis summary are shown below.

Author, year	M/A[1]	Primary outcome	N (approx.)	All IBD RR (95% CI)	Crohn's RR (95% CI)
Bernstein, 2009	M	IBD	21,500	**1.16** (0.73 - 1.77)	**1.15** (0.61 – 2.02)
Crockett, 2010	M	IBD	29,000	**1.68** (0.98 - 2.86)	**0.68** (0.28 – 1.68)
Etminan 2, 2012	M[2]	IBD	80,000	**0.62** (0.43-0.89)	*Not reported*
Alhusayen, 2013	M	IBD	1,700,000	**1.14** (0.92 - 1.41)	**1.17** (0.90 – 1.52)
Fenerty, 2013	A, PPT	IBD	175,000	**0.57** (0.28 - 1.16)	*Not reported*
Etminan, 2013	M	IBD	45,500	**0.99** (0.52 – 1.9)	**0.91** (0.37-2.25)
Rashtak, 2014	M	IBD	1000	**0.28** (0.1 - 0.8)	**0.29**[3] (0.03 - 2.8)
Racine, 2014	M	IBD	44,000	**0.74** (0.49 – 1.13)	**0.45** (0.24-0.85)
Sivaraman, 2014	A	UC, CD	500	*Not reported*	**4.8** (0.30 – 70)
Meta-analytic summary[4]			**2,100,000**	**0.87** (0.65 – 1.17)	**0.87** (0.59 – 1.28)

[1] Manuscript/Abstract, PPT=PowerPoint

[2] Online technical report

[3] Calculated from raw numbers supplied in paper

[4] Calculated with DerSimonian-Laird method. Profile likelihood showed similar results. Knapp-Hartung widened confidence limits by approximately 0.1 on each side.

As discussed in greater detail herein, the information learned from the aforementioned studies together with the testimony of Dr. Madigan and Dr. Goodman at the Kemp Hearing leads the court to conclude that there is no epidemiologic evidence to justify a reasonable inference that there is a causal link between Isotretinoin and CD. Nor is there any rational basis for Plaintiffs to resist the findings of all the epidemiological studies before the court, except for the Sivaraman Study, comprised of 509 patients. Plaintiffs' criticism of the studies relied upon by Defendant served to highlight the serious weakness of the single study upon which Plaintiffs rely, namely, insufficient numbers to warrant respect by the scientific community. (NOTE: Dr. Kornbluth and Dr. Madigan ignore the Sivaraman authors' own conclusions.)

B. Prodrome of CD and IBD

The prodromal period, namely, the length of time in between the first symptoms and a conclusive diagnosis of CD, was described at length by the parties' experts. In addition to the nine risk assessment epidemiological studies recited above, the court examined 10 studies regarding the prodrome of IBD. The chart below summarizes these studies.

Crohn's Disease Prodromal Period Studies

Study	Size (CD)	Prodrome	Data Source
Barratt	152	2 years (mean)	Single UK referral center
Burgmann	65 (30 w/o IBS)	10.1 years (mean) 7 years (median)	Manitoba IBD cohort study
Burisch	535	4.6 and 3.4 months (median—West/East Europe)	31 European centers
Chouraki	7409	3 months (median)	French IBD registry
Nahon	364	5 months (median)	Two French referral centers
Pieper	59	Various results by percentage (see attached)	Various medical practices in Germany
Pimentel	29	6.9 years (mean)	Single referral center
Romberg-Camps	448	5 months (median)	Dutch IBD registry
Vind	209	8.3 months (median)	Denmark cohort
Vivricka	932	9 months (median)	Swiss cohort study

As discussed herein, based upon the testimony presented, the court concludes that the results of the Pimentel Study are not sufficiently reliable science to permit submission to a jury. Plaintiffs' criticism of the studies relied upon by Defendant on the prodromal issue served to highlight the serious weakness of the single study upon which Plaintiffs rely, namely, insufficient numbers to warrant respect by the scientific community, compared to the large sample sizes of studies that do not support their argument.

C. Limitations of Adverse Event Reports (Med-Watch)

Throughout their testimony, Plaintiffs' experts made reference to spontaneous reports filed with the FDA. The FDA Adverse Event Reporting System (FAERS) typically yields information that is not evidentiary in a court of law. As the FDA itself notes, there are serious limitations to such information.

> Do FAERS Data Have Limitations?
>
> FAERS data do have limitations. First, there is no certainty that the reported event (adverse event or medication error) was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.
>
> FDA Adverse Event Reporting System (FAERS) (Last updated September 8, 2014), http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

In addition to the aforesaid concern, the FDA also noted in its "Guidance for Industry: Good Pharmacovigilance Practices Epidemiologic Assessment" [March 2005], at S125, 2.1, "Applying DPA to Longitudinal Data"

> In the context of spontaneous report systems, some authors use the term "signal of disproportionate reporting" (SDR) when discussing associations highlighted by DPA methods. In reality, most SDRs that emerge from spontaneous report databases represent non-causal effects because the reports are associated with treatment indications (i.e., confounding by indication), co-prescribing patterns, co-morbid illnesses, protopathic bias, channeling bias, or other reporting artifacts, or, the reported adverse events are already labeled or are medically trivial.

In addition to the FDA's concerns with regard to the limitations on spontaneous reports, there are concerns of Dr. Madigan himself as expressed in prior publications. In a scholarly text entitled *Quantitative Evaluation of Safety in Drug Development*, he and his colleagues state:

> While the spontaneous adverse event reporting system has value in generating hypotheses about potential associations, it has several limitations that make causal assessments difficult: voluntary reporting suffers from chronic underreporting and other biases, and the unknown nature of underlying population makes true reporting rates difficult to obtain and use for comparisons. It has been estimated that only about 1% of all adverse drug reactions and about 10% of all serious adverse drug reactions are reported (Furberg, et al. 2006) Reports are "usually based on suspicion, and may be preliminary, ambiguous, doubtful or wrong" (Meyboom, et al. 1999, Chapter 9, p. 143).

Additionally, there is the concern of potential abuse of the FAERS. As reported in a treatise entitled "Alleged Isotretinoin-Associated Inflammatory Bowel Disease: Disproportionate reporting by attorneys to the Food and Drug Administration Adverse Event Reporting System" prepared by D.J. Stobaugh, et al., published May 16, 2013, in the *Journal of the American Academy of Dermatology*, concerns of abuse of the filing system were raised. The authors analyzed 3.3 million(+) cases filed with the FAERS between 2003-2011 and queried "for IBD cases reported with Isotretinoin for a usage indication of acne." It was found that:

> There were 2,214 cases of IBD resulting from Isotretinoin. Attorneys reported 1,944 (87.8%) cases, whereas physicians reported 132 (6.0%) and consumers reported 112 (5.1%) cases (P value < .01). For the entire FAERS, only 87,905 of the total 2,451,314 (3.6%) reports for all drug reactions during the same time period were reported by attorneys (P value < .01). The signal inflation factor for IBD with Isotretinoin for attorney-initiated reports was 5.82, signifying a clear distortion.

The legal profession is a bulwark of our society, yet the courts should never underestimate the resourcefulness of some attorneys.

Finally, there are limited occasions in which the information derived from adverse event reports may be used as an integral link in a chain of evidence in support of a novel hypothesis of a causal relationship, but as will be shown, not in this instance.

D. Limitations of Case Reports.

The *Reference Manual* (p. 724) ranks case reports at the bottom of the medical evidence hierarchy. Such reports are typically based upon a relatively small number of individual patients and their particular anecdotes as reported by a treating physician. Such information can be extremely valuable in creating "signals" which may form the basis of a hypothesis, but such information is no more than hypothesis-generating and not capable of testing a hypothesis.

Despite Plaintiffs' efforts to characterize case reports as inherently valuable evidence, not everyone in the scientific community agrees. During his testimony, Dr. Kornbluth expressed very high regard for Dr. Brian G. Feagan stating that he is "extraordinarily well-respected" and further that he is "among the best around" in the field of gastroenterology. In *Gastroenterology & Hepatology* 9 (11) 752-753, November, 2013. Dr. Feagan expressed his opinion on case reports:

> Case reports or series are the lowest form of evidence available. Essentially, these reports are anecdotes. No control group exists; a case series cannot establish whether or not an association beyond chance exists. A more methodologically rigorous design is the case-control study in which a group of patients with a given condition are retrospectively matched for important variables, such as age and gender, to controls without the disease.

The FDA also has guidelines for the use of case reports. At page 7 of *Guidance for Industry-Good Pharmacovigilance*, the FDA says:

> For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product. To date, there are no internationally agreed upon standards or criteria for assessing causality in individual cases, especially for events that often occur spontaneously (e.g., stroke, pulmonary embolism). Rigorous pharmacoepidemiologic studies, such as case-control studies and cohort studies with appropriate follow-up, are usually employed to further examination the potential association between a product and an adverse event.

Finally, there are limited occasions in which the information derived from case reports may be used as an integral link in a chain of evidence in support of a novel hypothesis of a causal relationship, but as will be shown, not in this instance.

E. Limitations on Animal Studies.

With regard to animal studies, the *Reference Manual* states, at page 563:

> Animal studies have two significant disadvantages, however. *First*, animal study results must be extrapolated to another species – human beings – and differences in absorption, metabolism, and other factors may result in interspecies variation in responses. ... In general, it is often difficult to confirm that an agent known to be toxic in animals is safe for human beings. The *second* difficulty with inferring human causation from animal studies is that the high doses customarily used in animal studies require consideration of the dose-response relationship and whether a threshold no-effect does exists. Those matters are almost always fraught with considerable, and currently unresolvable, uncertainty.

Because dogs are also mammals - their intestines are similar to those of humans - the results of such testing may be helpful in determining whether or not a particular chemical substance can cause harm to the intestines. That said, the results of the tests proffered by Plaintiffs' experts, namely, those performed by Defendant, provide no meaningful support for Dr. Kornbluth's hypothesis. Whether or not any of the harm caused by Isotretinoin to the dogs' intestines is permanent cannot be known for two reasons: first, the dogs in the experiment are dead, euthanized upon completion of the testing; and second, dogs cannot develop IBD. Both Dr. Kornbluth and Dr. Oliva-Hempker agree that IBD is not a condition from which dogs ever suffer.

Finally, there are limited occasions in which the information derived from animal studies may be used as an integral link in a chain of evidence in support of a novel hypothesis of a causal relationship, but as will be shown, not in this instance.

F. Consideration of Late Submissions Made By Plaintiffs' Counsel. Subsequent to the close of the Kemp hearing, Plaintiffs' counsel saw fit to make two submissions to the court. The first is under cover of the Certification of David R. Buchanan, Esquire, dated February 11, 2015 and filed February 12, 2015 shortly after the hearing concluded. Said submissions comprise four judicial decisions which this court has previously read. The second submission is under cover of the Certification of Michael L. Rosenberg, Esquire, dated February 12, 2015. Said submissions comprise deposition transcripts of portions of testimony of Dr. Alan Bess, Dr. Daniel Reshef, Dr. Ellison Kendall and Dr. Urs Bernard Niedhauser. The court has reviewed these submissions. When said information is considered in the totality of the evidence presented at the Kemp hearing, it does not alter the court's findings or conclusions.

VII. DEFICIENCIES IN PLAINTIFFS' METHODOLOGY.

As the proponent of the evidence on general causation, "The plaintiff bears the burden of establishing admissibility." *Kemp, supra,* 174 N.J. at 429. As discussed herein, the testimony of the Plaintiffs' experts suffers from multiple deficiencies, the most salient of which is their finely-tuned selectivity of the evidence upon which they rely. 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. While both Plaintiffs' experts are eminently qualified, their reasoning and methodology is slanted away from objective science and in the direction of advocacy. It is this court's conclusion that the opinions expressed by Plaintiffs' experts are motivated by preconceived conclusions, and that they have failed 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.

As instructed by our Supreme Court in *Landrigan, Id.* at 420, the trial court must make an "evaluation of the validity of ... the studies on which [the experts] relied," and, in determining admissibility, must "examine each step in [the expert's] reasoning." *Id.* at 421. The court proceeds to the analysis with respect to Plaintiffs' reliance upon the Sivaraman Study and the Pimentel Study.

A. Reliance Upon Sivaraman Study

(1) Upon consideration of all the experts' testimony, the aspect of this study which the court found puzzling was the meaning ascribed to it by Plaintiffs' experts. Curiously, they interpret the results of the study contrary to the authors' own stated conclusions. The scientists who prepared this one-page abstract stated their "purpose" as follows: "We conducted a case-control study in a pediatric and adult population to determine whether risk for IBD from Isotretinoin is modulated by antibiotic exposure." The abstract's "conclusion" reads: "Risk of IBD from Isotretinoin is modulated by antibiotic exposure. *Isotretinoin exposure does not appear to confer risk for either UC or CD independent of antibiotic exposure."* (emphasis added) How can that conclusion possibly offer support for a causative risk association between Isotretinoin and CD? It clearly does not. Additionally, as the study's authors noted in their "results" portion of the abstract, after adjusting for antibiotic exposure, the risk for IBD

following Isotretinoin exposure lost any statistical significance. If it lost "statistical significance," how/why do Plaintiffs believe that it is of any value as a risk assessment? Clearly, it is not.

(2) The data utilized in the Sivaraman Study was collected via questionnaires which are subject to recall bias and poor recollection.

(3) This was not a population-based study but rather a control group and as Defendants' experts note, a rather unusual and limited control group.

(4) The report of this "Study" is a one-page abstract, published at one-quarter page, without footnotes, in the *American Journal of Gastroenterology. If* this abstract were peer-reviewed, it was at a different level than the review accorded a formal published article. Neither Dr. Madigan nor Dr. Kornbluth made any effort to speak with the authors or learn anything more about this study.

(5) The number of subjects in the study - 509 – is of extremely limited weight and value as an epidemiological study and has little to no influence when included in a meta-analysis.

(6) Dr. Kornbluth and Dr. Madigan repeatedly rely on a higher unadjusted result for the odds ratio of 5.6 (none of the larger, population-based studies come close to that number for an odds ratio) that does not eliminate the risk that antibiotics would bias the result. The reliance on the higher number (5.6) stands in opposition to the authors' own methods and conclusions. In the absence of a meaningful scientific explanation for doing so, the court must conclude that this is pure advocacy.

In summary, as used by Plaintiffs' experts to support risk assessment, the Sivaraman Study is a long way from "compelling evidence" because it is not supported by "prolonged, controlled, consistent and validated experiences." *Rubanick, supra,* 125 *N.J.* at 446. Additionally, the quality of this Study is "[not] of a kind on which such experts ordinarily rely." *Landrigan, supra,* 127 *N.J.* at 417. The unsound nature of Plaintiffs' methodology in relying upon such a study becomes readily apparent when compared with the population studies, involving hundreds of thousands of subjects presented to the court. Plaintiff's rationalization for ignoring the other studies is assertedly their failure to account for a lengthy prodrome of CD. Yet here again, Plaintiffs' experts engage in their finely-tuned selectivity of the evidence by disregarding eight of nine prodromal studies.

B. Reliance Upon Pimentel Study

(1) As noted above, the prodromal period for CD is relevant to the court's analysis. Regrettably, Plaintiff's experts, disregarded large, population-based studies in favor of a single, much smaller study. The Pimentel Study comprises a total of 76 subjects who were referred from the community and presented to the Cedars-Sinai IBD Center and asked to participate in the study. As noted by Dr. Goodman, there are two significant flaws undermining its credibility: (1) the size of the study – a grand total of 76 subjects, focusing on 26 of them diagnosed with CD - from which supposedly meaningful conclusions are derived; and (2) all of the subjects were referred from other gastroenterologists, apparently because they were found difficult to manage or diagnose. As expressed by Dr. Goodman, the accepted standards of epidemiology show that this study has no meaning because the subjects come from a narrow population base rather than a broad one, which is necessary for it to have scientific credibility.

(2) The fundamental flaw of the Pimentel Study is that the referrals amounted to cherry-picking the subjects. As described by Dr. Goodman, in order to be a valid epidemiology study on the prodromal period, far greater efforts had to have been made to capture as many patients as possible, have them properly diagnosed, and then do an estimate of the time between the onset of symptoms to the diagnosis as close as possible. The studies disregarded by Plaintiffs' experts made the effort to do so. In short, as used by Plaintiffs' experts, the Pimentel Study is not based upon "prolonged, controlled, consistent and validated experiences." *Rubanick, supra,* 125 *N.J.* at 446. This is readily apparent when the contents of that study are juxtaposed with the other nine studies. What's more, the quality of this study is "[not] of a kind on which such experts ordinarily rely." *Landrigan, supra,* 127 *N.J.* 417.

C. Net Worth of Sivaraman and Pimentel

(1) Plaintiffs' reliance upon a single study of 509 subjects in an effort to inform the discussion on general causation, and again upon a single study totaling 76 subjects to define the prodromal period of CD demonstrates to this court the artistry of "the self-validating expert, who uses scientific terminology to present unsubstantiated personal beliefs." *Landrigan, supra,* 127 *N.J.* at 414. The reliance upon these two studies is fatal and reveals the lengths to which legal counsel and their experts are willing to contort the facts and torture the logic associated with Plaintiffs' hypothesis.

(2) The scientific literature does not support reliance upon such insignificant studies to arrive at conclusions. As advised by not only the *Federal Manual* and defense witness Dr. Goodman, S.C. Ng, et al. and Ponder and Long (see "V, C" hereinabove) conclude that epidemiological studies based upon a large number of participants are necessary to learn more about IBD. Moreover, Plaintiffs' contention that their experts examined "the same lines of evidence" and simply draw different conclusions lacks credibility because they are not utilizing the same methodology as other experts in their field. Their method is one of self-validating advocacy.

(3) With regard to these two studies, one wonders whether Dr. Kornbluth or Dr. Madigan would cite them as meaningful any place but a court room. Having observed both gentlemen and their apparent pride in their professional accomplishments, it seems unlikely that Dr. Kornbluth would stand before a symposium of his colleagues at the North American Conference of Gastroenterology Fellows, or that Dr. Madigan would appear before the Institute of Mathematical Sciences, and rely upon these studies as defining treatises.

D. Dr. Madigan's Testimony

(1) The "Sivaraman Study" is a cornerstone-like document for the Kornbluth hypothesis, which Dr. Madigan embraced unreservedly, utilizing it as a foundation for his methodological construct. Had he chosen to do so, Dr. Madigan could have made an effort to pool the quantitative results of the several studies in pursuit of a more precise estimate of the risk assessment. He did not. Rather than conducting a meta-analysis himself of all the risk assessment studies, and possibly getting "closer to the truth," he chose to disregard eight of them. In doing so, he ignored the knowledge learned from studying approximately 2,100,000 subjects. Instead he relies upon a study comprised of 509 people. He opined that this single-page abstract, never reduced to a formal peer-reviewed article, provides a reliable basis for arriving at an informed risk assessment. The Sivaraman Study falls far short of reliable evidence and doesn't begin to approach "prolonged, controlled, consistent, and validated experiences" of scientific research. *Rubanick, supra,* 125 *N.J.* at 446.

(2) As to Dr. Madigan's reliance upon the Pimentel Study and disregard of the other nine studies, this is not valid methodology. Rather than pooling the quantitative results from all 10 of the prodromal studies and conducting a meta-analysis of his own, and possibly getting

"closer to the truth," he simply disregards nine of them. In doing so, he ignores the knowledge gleaned from scientific assessments involving approximately 10,000 subjects and relies solely upon the results of information received from 26 subjects.

(3) Dr. Madigan's opinions aren't "methodology based," but rather are conclusion-driven. This is an expert on a mission. As cautioned by our Supreme Court, trial courts must attend to "the hired gun phenomenon." *Rubanick, supra,* 125 *N.J.* at 453. Dr. Madigan's role was to scrutinize "the statistical power of extant observational studies" and to provide an expert opinion utilizing plausible-sounding statistical challenges to explain away the results of the large population-based observational studies on risk assessment and the prodromal period. Without the testimony of Dr. Madigan, Plaintiffs are left with the highly informative significant results of the population-based epidemiological studies. Dr. Madigan was needed to clear the way for Dr. Kornbluth's hypothesis and that was the role he played, without regard to whether or not his efforts led the discussion any closer to scientific truth.

E. Dr. Kornbluth's Hypothesis and Methodology

(1) Dr. Kornbluth wants to have it both ways. First, he wants the court to reject the best evidence available because he says it is flawed. Second, he wants the court to accept inferior evidence at the bottom of the medical evidence hierarchy because it is all that he can find to support his hypothesis of causation.

Dr. Kornbluth's written report itself confirms that his hypothesis is a muddle of ambiguities and that his report camouflages mere speculation as true science.

a) "Acute injuries to the epithelial barrier between the intestinal lumen and deeper sections of the intestinal surface, **may allow entry of** bacteria initiating an aberrant immune response that **can potentially perpetuate** a chronic inflammatory state." (Sartor B. Nature Clin Prac Gastro Hepatol 2006; 3:390). Report of Arthur Asher Kornbluth, M.D., *Accutane and Crohn's Disease*, Dated December 15, 2014, page 5.

b) "This study found that increased generation of retinoic acid ***may contribute*** to pathology by maintaining inflammatory characteristics of newly recruited cells to intestinal areas affected in patients with Crohn's disease." (Sanders T J. Gastro 2014; 146:1278-1288). *Ibid.*

c) "These recent findings reflect a further mechanism through which elevated levels of retinoic acid ***may contribute*** to the pathogenesis of Crohn's disease." *Id.* at 6.

d) "As discussed above, luminal contents ("antigens") from the small intestine ***may be sampled*** by antigen presenting cells and be presented to "naïve" T cells." *Id.* at 8.

e) "When a specific antigen is recognized by a naïve T-cell, ***it may become activated*** into a pro-inflammatory cell." *Id.* at 8.

Courts may not permit juries to consider testimony of medical causation that is phrased in terms such as "may allow," or "may contribute to," or can potentially perpetuate," or "it may become activated" because they are mere conjecture. Regardless of the nature of the claims or the status of the parties, experts may not speculate before a jury. "Subjective speculation that masquerades as scientific knowledge does not provide good grounds for admissibility of expert opinions. See *Glastetter v. Novartis,* 252 *F. 3d* 986, 989 (8th Cir. 2001).

(2) Dr. Kornbluth is highly selective with regard to those scientific opinions he finds reliable (See "VII, A & B" above). The most startling illustration is his description of the "Sivaraman Study". As stated by Dr. Kornbluth, it was a "poster presentation" at a meeting of the American College of Gastroenterology, which he characterized as akin to a "glorified" bulletin board where participants can speak with the author, yet he never spoke with the authors at the meeting, or any time later. The study comprised 509 subjects and then was adjusted "for antibiotic exposure." As explained by Dr. Kornbluth, "because they had shrunk the number of patients in the analysis, it no longer reached statistical significance." In short, Dr. Kornbluth relies on selected aspects of an abstract while standing at odds with the authors' methods and conclusions.

(3) Dr. Kornbluth's discussion of his hypothesis for the biological mechanism of the development of CD as caused by Isotretinoin falls far short of being "compelling." His basis for this discussion are the medications Natalizumab and Vedolizumab. He attempts to extrapolate causation of CD by Isotretinoin by discussing treatment of CD by these other medications. Dr. Oliva-Hempker explained the inherent weaknesses of trying to rely upon the data on Natalizumab and Vedolizumab as being probative of causation. In essence, treating a "pathway" that develops once a disease occurs, does not mean that that a particular treatment mechanism informs as to the original cause of the disease. She also pointed out that this hypothesis is contrary to a significant body of scientific literature showing that Retinoic acid is actually anti-inflammatory and helps in regulation.

A comparison of Dr. Kornbluth's testimony of February 3, 2015, 233:20 thru 240:13 and Dr. Oliva-Hempker's testimony of February 9, 2015, 58:4 thru 59:19 reveals the tortured nature of Dr. Kornbluth's methodology. Reliance upon whatever treatment value Natalizumab and Vedolizumab may have upon CD is misplaced. Implicit in Dr. Kornbluth's methodology is a fundamental assumption, namely, that retinoic acid causes intestinal inflammation – but the scientific literature reveals a significant dispute on that assertion. In short, his assumption, and the use he makes of it, are not "data and information of the type reasonably relied upon by experts in the scientific field." *Rubanick, supra,* 125 *N.J.* at 449.

(4) Dr. Kornbluth's testimony is replete with what can be described as *convenient assumptions.* When he needs to bridge an analytical gap in his methodology he assumes facts, events and conclusions as he wants them to be in support of his hypothesis. By way of illustration, the court considers review of his testimony on cross examination on February 4, 2015, pages 106 through 165. The court notes that in response to counsel's questioning regarding the results of various studies, Dr. Kornbluth assumed: (a) that all the patients in the two studies upon which he relied filled out their questionnaires correctly; (b) despite the fact that the authors of the Sivaraman Study got it wrong as to their adjustment for antibiotics, he assumed they got everything else correct; (c) he assumed that in the Rashtak Study, the patients with Accutane exposure were followed for less time than the control group; and (d) he assumed the size of the doses of Accutane given to the subjects in various studies.

In short, Dr. Kornbluth's reasoning is a string of ambiguities held together by two insignificant and misused studies, plus convenient assumptions to bridge any analytical gaps that might arise along the way. Such contrived reasoning is not supported by the scientific community as a reliable basis for making causal determinations. His testimony falls far short of "sound, adequately-founded scientific methodology involving data and information of the type reasonably relied upon by experts in the scientific field." *Rubanick, supra,* 125 *N.J.* at 449.

Although there are other issues raised at the Kemp hearing which the court believes demonstrate additional defects in the hypothesis of general causation advanced by Plaintiffs, little is to be gained from detailing them.

VIII. RULING

It is one thing to stand alone in the world of science, advancing a hypothesis that others do not accept. It is quite another thing to advance a hypothesis that can only be supported by disregarding valid scientific research. The court embraces its obligation to be flexible in applying scientific evidence to novel personal injury claims falling within the penumbra of "toxic torts" nonetheless, such claimants have a reciprocal obligation to be mindful of the standards of the scientific community. The foundations of the hypothesis for general causation of an injury cannot be contrived; they must be based upon sound methodology sufficiently reliable to be presented to a jury.

Finally, coursing through Plaintiffs' presentation is a refrain that is a ruse. Repeatedly, counsel for the Plaintiffs and their witnesses spoke of "lines of evidence," emphasizing that their experts examined "the same lines of evidence" as did the experts for the Defense. Counsels' sophistry is belied by the fact that the examination of the "lines of evidence" by Plaintiffs' experts was highly selective, looking no further than they wanted to – cherry picking the evidence – in order to find support for their conclusion-driven testimony in support of a hypothesis made of disparate pieces, all at the bottom of the medical evidence hierarchy. This crafty stratagem cannot bridge the analytical gaps inherent in Plaintiffs' hypothesis.

For the reasons stated herein, the Defendant's Motion to bar the testimony of Dr. Arthur Kornbluth and Dr. David Madigan is hereby GRANTED. An Order accompanies this Memorandum of Decision. Defense counsel is instructed to prepare a form of Order reciting those lawsuits effected by this ruling – including Captions and Docket Numbers - and submit the same to the court on or before March 6, 2015. Said Order will not be entered until Plaintiffs' counsel have an opportunity to be heard on the form of the same, particularly, the precise Captions and Docket Numbers.

Nelson C. John

NELSON C. JOHNSON, J.S.C.

Date of Decision: 2/20/15