UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF MISSOURI
WESTERN DIVISION

SADIE MILLER, **Plaintiff,** **v.** **BAYER HEALTHCARE PHARMACEUTICALS INC.; BAYER PHARMA AG; and BAYER OY,** **Defendants.**	**CASE NO. 4:14-cv-00652-SRB**

PLAINTIFF'S SUGGESTIONS IN OPPOSITION TO BAYER DEFENDANTS' OMNIBUS MOTION TO EXCLUDE GENERAL CAUSATION AND LABELING OPINIONS

Junk science. That's what *Daubert* is intended to exclude. Not scientific conclusions that a party disagrees with; not scientific conclusions that a court disagrees with; and not even scientific studies that have biases, limitations or deficiencies (because, as Bayer's experts freely admit, they all do!). Instead, "[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." *Daubert v. Merrell Dow Pharms.*, 509 U.S. 579, 596 (U.S. 1993) (citing *Rock v. Arkansas*, 483 U.S. 44, 61 (1987)). But Plaintiff does not even rely on shaky evidence in this case. Far from "cherry-picking" the scientific evidence as Bayer suggests, Plaintiff's experts have considered *all* evidence on the subject of an association between Mirena and pseudotumor cerebri/intracranial hypertension ("PTC/IH") and it happens to support their conclusions. Bayer cannot point to a single piece of evidence regarding the potent synthetic hormone in Mirena (levonorgestrel) and PTC/IH that concludes there is ***no*** association.

Only two epidemiological studies have ***ever*** been performed to study the association between levonorgestrel and PTC/IH. Both involved the Mirena. One was performed by Dr. Etminan (a former expert in this case who Bayer has viciously attacked as incompetent, dishonest and unreliable-- at least with respect to the parts of his opinions that Bayer does not like). The other study was performed by a group of well-respected, independent clinician-researchers at the University of Utah, including one of the most prominent members of the ophthalmological community, Dr. Kathleen Digre (hereinafter, the "Rai/Digre Study"). Those independent researchers concluded:

> ***Exposure to an LNG-IUS was significantly associated with the development of IIH*** (OR 7.7, 95% CI 3.2-16.4, p<0.001); the prevalence of IIH was 0.18% in the LNG-IUS population (8/4408, 95% CI 0.07-0.35) versus 0.02% in the non-LNG-IUS population (51/216555, 95% CI 0.01-0.03). Of those IIH patients not on an LNG-IUS, 9 (15%) were on another contraceptive and 42 (71%) were not on any contraceptives. All LNG-IUS users who developed IIH manifested symptoms

> while the device was still in situ. There were no significant differences between LNG-IUS users and non-users in terms of age, body mass index, recent weight gain, or presenting signs and symptoms.

Rai et al., *The relationship between the levonorgestrel-releasing intrauterine system and idiopathic intracranial hypertension,* 56 INVEST. OPHTHALMOL. VIS. SCI. 2228 (2015) (emphasis added) (hereinafter "Rai/Digre Study"), Ex. A42.

The Rai/Digre study's 7.7 odds ratio[1] is high enough to establish causation ***on that basis alone***. *See Manko v. United States*, 636 F. Supp. 1419, 1434 (W.D. Mo. 1986) (explaining that "[a] relative risk greater than "2" means that the disease more likely than not was caused by the even). Reference Manual on Scientific Evidence 3d, p. 612 (2001) ("[W]hen epidemiologic studies find that exposure to the agent causes an incidence in the exposed group that is more than twice the incidence in the unexposed group (i.e., a relative risk greater than 2.0), the probability that exposure to the agent caused a similarly situated individual's disease is greater than 50%. […] Courts, thus, have permitted expert witnesses to testify to specific causation based on the logic of the effect of a doubling of the risk."), Ex. A31.

But Plaintiff's experts did not start and stop with the Rai/Digre study. As each testified, their conclusions are based upon the body of the evidence as a whole, including all the things that medical professionals, clinicians and research scientists review in their daily practices to reach such conclusions (i.e., literature reviews, case studies, spontaneous adverse event reports and even drug product labeling). As one court correctly articulated:

> Daubert does not require proof to a certainty, or even proof convincing to the trial judge. The trial judge is not required to find that the proffered opinion is scientifically correct, but only that it is trustworthy because it is tied to good scientific grounds. What Daubert does require is that the expert's opinion be based on sound methodologies of the type used by experts in the field in which

[1] Relative risk is the ratio of the incidence rate of disease in exposed individuals to the incident rate in unexposed individuals. Ex. A31 at 627. "A relative risk that is less than 1.0 means that exposure is associated with the absence of disease, and a relative risk that is greater than 1.0 means that exposure is associated with disease." *Dunn v. Sandoz Pharms. Corp.*, 275 F.Supp.2d 672, 680 fn. 7 (M.D.N.C. 2003)). An odds ratio "approximates the relative risk", and the distinction is not significant where a disease is rare. Ex. 31 at 568.

> the opinion is offered. There can be little question that scientists routinely use animal studies, case reports, and pharmacological comparisons of similar classes of drugs to infer conclusions, which are expressed in peer-reviewed journals and textbooks. Unquestionably, epidemiological studies provide the best proof of the general association of a particular substance with particular effects, but it is not the only scientific basis on which those effects can be predicted. **In science, as in life, where there is smoke, fire can be inferred, subject to debate and further testing.**

Brasher v. Sandoz Pharms. Corp., 160 F. Supp. 2d 1291, 1296 (N.D. Ala. 2001) (emphasis added). Likewise, in this case, Plaintiff's experts have reliably applied scientific principles to reach their conclusions that the Mirena levonorgestrel-releasing IUD more likely than not can cause PTC/IH. Accordingly, Bayer's motion should be denied.

FACTS

Pseudotumor Cerebri/Intracranial Hypertension ("PTC/IH") is a serious condition involving increased intracranial pressure caused by excess build-up of cerebrospinal fluid around the brain. The condition mimics a brain tumor. A cardinal sign of PTC/IH is an ophthalmologic condition known as papilledema, which is a swelling of the optic nerves. PTC/IH can lead to permanent loss of vision; can cause debilitating headaches, tinnitus, fatigue, and other such symptoms; and may require surgery (even brain surgery) to alleviate symptoms. Tang Rpt. at 2-3, Ex. N1. PTC/IH patients have also been known to develop severe depression, become suicidal, and are expensive to treat.[2] It is a life-altering condition with drastic consequences for patients and their families. The term pseudotumor cerebri (literally translated as "false brain tumor") is more or less synonymous with many other terms for the same condition, including "Idiopathic Intracranial Hypertension", "Secondary Intracranial Hypertension", and "Benign Intracranial

[2] Daniels et al., *Profiles of Obesity, Weight Gain, and Quality of Life in Idiopathic Intracranial Hypertensionv (Pseudotumor Cerebri)*, 143 Am. J. Ophthalmol. 635, 638 fig. 3 (2007), Ex. A25; Friesner et al., *Idiopathic intracranial hypertension in the USA: the role of obesity in establishing prevalence and healthcare* costs, 12 Obesity Rev. e372–e380 (2011), Ex. A29; Kleinschmidt et al., *Idiopathic intracranial hypertension: relationship to depression, anxiety, and quality of life*, 54 Neurology 319–324 (2000), Ex. A14.

Hypertension". *See* ICD-9 2015, Ex. C2. It may also be called "Medication-Induced Intracranial Hypertension" or "Iatrogenic Intracranial Hypertension". Treating physicians and researchers, including neuro-ophthalmologists, often use these terms interchangeably to describe essentially the same syndrome of excessive cerebrospinal fluid pressure, regardless of the cause. Ross Dep. 22:18-21, Ex. M3; Tang Rpt. at 2, Ex. N1.

1. Plaintiff Sadie Miller

Ms. Miller received a Mirena IUD for contraception on January 25, 2013. SMiller-PPR-0001821, Ex. F1. After experiencing bleeding and pelvic pain, the device was found to be in the wrong position and was replaced on May 24, 2013. *Id.*, at SMiller-PPR-000196.

Just three months after her second Mirena insertion, Ms. Miller began experiencing bleeding; chest pains; lightheadedness; pain in the arm, neck, and back of the head; and severe headaches associated with tinnitus and blurry vision in both eyes. *Id.*, at SMiller-PPR-000210, SMiller-PPR-000228 (record dated 08/11/2013, headache and associated symptoms "onset/duration: 2wk"). On August 1, 2013, Ms. Miller "requested removal of the IUD because of adverse effects related to the device." *Id.*, at SMiller-PPR-000210.

After diagnosis of papilledema and associated symptoms, Ms. Miller was referred to neurology and underwent imaging, lumbar puncture, and cerebrospinal fluid (CSF) studies. *Id.*, at SMiller-000027. Ms. Miller was diagnosed with "Atypical pseudotumor cerebri" as she did not fit the classic risk factors for the disease, and "her symptoms quite precipitous and perhaps associated with the Mirena IUD." *Id.*, at MIR-PPR-000030.

Unfortunately, Ms. Miller continued to experience symptoms including headaches, whooshing noises, and fluctuating visual acuity, despite removal of Mirena, medication therapy and weight loss attempts. However, continued improvement and eventual resolution was noted in her visual fields and imaging of the optic nerves. SMiller-UKansasMC-MD-000086. Ex. F2.

2. Plaintiff's Experts' Qualifications

Plaintiff has disclosed four extremely well-qualified experts. Three of them are practicing medical doctors (Tang, Ross and Fraunfelder) in addition to their many other qualifications, and their pharmacology expert teaches medical students in the areas of both pharmacology and neurology. Each has opined that Mirena more likely than not causes or contributes to the development of PTC/IH, based on their review of the available scientific evidence. They have also offered opinions that the complete lack of a warning for PTC/IH on the Mirena label makes it inadequate for both prescribing physicians, end user patients, and even physicians who diagnose and treat PTC/IH.

Without question, Dr. Fraunfelder is among the most well-respected researchers on ocular side effects of drugs in the entire world. He is the Chairman of the Mason Eye Institute at the University of Missouri, where he serves as a Distinguished Professor, and is the Clinical Director of the University of Missouri's Department of Ophthalmology. He is the only ophthalmologist consultant for the World Health Organization's ("WHO") Uppsala Monitoring Centre, which collects global data on drug adverse effects. Fraunfelder Dep. 19:17-22:4, Ex. G3. He literally wrote the book on drug-induced ocular side effects, which is the most complete listing of known ocular side effects available in print. *See* Fraunfelder et al., Drug Induced Ocular Side Effects (2015 7th Ed.) (excerpted), Ex. A39. Dr. Fraunfelder co-authors two others, including one on ocular toxicology. Fraunfelder CV p. 4, Ex. G2. Dr. Fraunfelder has won numerous awards and has served as an editorial board member and reviewer for several prominent ophthalmological publications. *Id.* at 3-4.

After obtaining his medical degree, Dr. Fraunfelder completed two residencies from 1995 to 2000, including an ophthalmology residency at the University of Washington Medical Center in Seattle, Washington, having already completed an internal medicine internship in 1994-

1995. Fraunfelder Dep. 16:16-18:1, Ex. G3. Dr. Fraunfelder also completed fellowships with the Casey Eye Institute in Portland, Oregon, and the World Health Organization ("WHO"), the Food and Drug Administration ("FDA"), and Alcon Pharmaceuticals, which specifically emphasized spontaneous reporting systems and pharmacovigilance. *Id.*, at 18:7-22:4; Fraunfelder CV p. 2, Ex. G2. He has been a board certified ophthalmologist since July 2002. Fraunfelder CV p. 1, Ex. G2. Dr. Fraunfelder has been practicing medicine in the ophthalmological specialty since 1997, providing him with nearly 20 years of experience. *Id.* at 1-2. He has taught medical students and residents since 2001. *Id.* at 1. Dr. Fraunfelder has also published more than 90 peer reviewed articles on ophthalmology. *See id.* at 5-26.

Dr. John Maggio is a pharmacologist at the University of Cincinnati, having obtained a Ph.D. in organic chemistry from Harvard University. Maggio CV p. 1. He has taught biological chemistry and pharmacology for over 30 years. *Id.* He completed post-graduate studies at both Yale and Cambridge in the areas of Neurochemical Pharmacology and Neuropsychopharmacology. *Id.* He has authored more than 100 peer reviewed publications. *Id.* at 2. Dr. Maggio has taught neurology at Harvard Medical School since 2007. *Id.* at 1.

Dr. David Ross, who is board certified in internal medicine and teaches at George Washington University Medical School, has ten years of experience at the FDA. Ross Rpt. at 2, Ex. M1; Ross CV p. 1-2, Ex. M2. He also has a Ph.D. in Biochemistry. Ross CV p. 1, Ex. M2. At the FDA, he served in progressively responsible positions until finally becoming the Associate Director for Regulatory Science in the Office of Oncology Drug Products (OODP) at the FDA's Center for Drug Evaluation and Research (CDER). *Id.* at 2. Among his relevant experience at the FDA, Dr. Ross's responsibilities included the review of New Drug Applications (NDAs) and Investigational New Drug Applications (INDs) for multiple

pharmaceutical products in a broad range of therapeutic areas. Ross Report p. 3, Ex. M1. Dr. Ross is also the Director of HIV, Hepatitis, and Public Health Pathogens Programs for the United States Department of Veterans Affairs (VA). *Id.* at 2. In this role, he provides "guidance on policy programs and products related to issues involving clinical public health, that is, public health matters that are relevant to clinical providers within the VA." *Id.* He has published 26 peer-reviewed articles, authored or edited two books, and has made numerous presentations on topics related to his work at the FDA. Ross CV p. 3-11, Ex. M2.

Finally, as conceded by Bayer, Dr. Rosa Tang certainly has "relevant experience with IIH." [DN 66] at 13. Dr. Tang possesses an extensive clinical and research background in the diagnosis and treatment of PTC/IH. 05/10/2016 Tang Dep. 235:5-236:2; 285:13-23, Ex. N3. She is currently the Co-Director of MS Eye Care at the University of Houston; Director of Neuro-ophthalmology of Texas, PLLC; Director of Eye Wellness Center - Houston; and a Clinical Assistant Professor of Neurosurgery at University of Texas, Houston. Tang 02/08/15 CV, Ex. N2. Her several advanced degrees include a Doctor of Medicine and a Masters of Public Health. *Id.* After medical school, Dr. Tang completed a residency in internal medicine at John Sealy Hospital - University of Texas Medical Branch, and a residency in ophthalmology at Jackson Memorial Hospital - University of Miami. *Id.* Subsequently, she completed a fellowship in neuro-ophthalmology at Baylor College of Medicine, one of the nation's preeminent institutions. She has practiced medicine, taught, and researched medicine for over 35 years.

3. Epidemiological Evidence Regarding General Incidence of PTC/IH and Risk Factors

a. Epidemiological Evidence Supporting Causation is the Same Kind as Normally Relied Upon in the Scientific Community.

Bayer's experts rely heavily on "general incidence" PTC/IH epidemiology studies to try to undermine Plaintiff's case, particularly with respect to Bayer's efforts to blame Plaintiff's

body weight as the causal factor. Like the Rai/Digre study, this "general incidence" and "risk factor" epidemiological evidence comes from retrospective studies where a small number of cases and controls are identified and then compared to a large database of anonymized data.[3] Like the Rai/Digre study, each of these studies has its own set of biases, limitations and deficiencies. Yet, these epidemiological studies on general incidence and risk factors (none of which studied levonorgestrel specifically) have been treated as scientifically sound by Bayer, Bayer's experts, and the entire scientific community. Thus, epidemiological evidence of this type is generally accepted among PTC/IH researchers despite potential biases and limitations common among these types of studies.[4] Other than Bayer and their paid consultants, no independent scientist has treated the Rai/Digre study as unreliable junk science.

b. Risk Factors Commonly Accepted by the Scientific Community.

In addition to female sex, childbearing age, and overweight, there are many factors also thought to be causally associated with PTC/IH. For example, Dr. Deborah Friedman, Bayer's consulting expert, has stated: "Among the many exogenous agents associated with intracranial hypertension**, the best evidence exists for** [...] **levonorgestrel contraceptive system**." Deborah Friedman, *Idiopathic Intracranial Hypertension*, 11 Current Pain and Headache Reports 62, 67 (2007) (emphasis added), Ex. A26. Like the risk factors discussed by Bayer (sex, age, and

[3] *See, e.g.*, Durcan et al., *The Incidence of Pseudotumor Cerebri Population Studies in Iowa and Louisiana*, 45 Arch. Neurol. 875, 875 (1988) (sent postcards to doctors to identify 27 cases, and used census data to generate incidence rates), Ex. A1; Radhakrishnan et al., *Epidemiology of idiopathic intracranial hypertension: a prospective and case-control study*, 116 J. Neurol. Sci. 18, 19-20 (1993) (identified 40 cases from ophthalmology and neurology clinics in Libya, then compared to Libyan census data, 40 controls related to the patients, and 40 controls recruited from around the hospital), Ex. A5; Radhakrishnan et al., *Idiopathic Intracranial Hypertension (Pseudotumor Cerebri): Descriptive Epidemiology in Rochester, Minn, 1976 to 1990*, 50 Arch. Neurol. 78, 78-79 (1993) (identified 9 cases from medical records index, then used census data to generate incidence rates), Ex. A4; Daniels et al., *Profiles of Obesity, Weight Gain, and Quality of Life in Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)*, Am. J. Ophthal. (2007) (used 34 IIH patients identified by 7 researchers as cases, 41 non-IIH neuro-ophthalmology patients identified by the same researches as matched controls, and compared them to anonymized data on quality of life), Ex. A25.

[4] *See, e.g.*, Deborah Friedman, *Medication-Induced Intracranial Hypertension in Dermatology*, 6 Am. J. Clin. Dermatol. 29, 30 (2005) (citing the Durcan and Ireland studies), Ex. A20.

overweight), the underlying mechanisms for the other risk factors are poorly understood. Similarly, there is no known mechanism for the role of obesity, overweight, recent weight gain, and female sex in causing PTC/IH; the belief that these factors cause PTC/IH is based solely on the strength of epidemiological associations.[5] It has been noted, however, that alterations in sex hormones, again based on PTC/IH's predilection for post-pubescent women, is a plausible disease mechanism.[6] In the case of Vitamin A toxicity and hyperaldosteronism, however, a biological mechanism has been more concretely demonstrated.[7] *See* Maggio Report, p. 41-43 (describing a mineralocorticoid mechanism based on research by Salpietro et al.), Ex. J1.

4. The Evidence Supporting a Causal Role for Mirena and PTC/IH.

The evidence supporting the role of the Mirena levonorgestrel-releasing IUD in causing or contributing to PTC/IH is both long-standing and wide-ranging. It encompasses: 1) evidence since the early 1990s that PTC/IH was associated with Mirena's levonorgestrel-releasing predecessor, Norplant; 2) numerous case reports and spontaneous reports, which have resulted in five different internal company safety signal assessments; and 3) epidemiological evidence showing that there is a 7.7 increased risk of developing PTC/IH with Mirena.

a. Evidence from Norplant and Scientific Consensus that an Association Exists

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[5] Chen & Wall, *Epidemiology and Risk Factors for Idiopathic Intracranial Hypertension*, 54 Int. Ophthalmol. Clin. 1, 4-5 (2014) ("Given the relatively high prevalence of obesity in IIH patients, weight clearly plays a role in the disease process. […]Although obesity is clearly associated with IIH, the mechanism of how it may cause IIH is unknown. Sex is the other obvious risk factor because over 90% of patients affected with IIH are women. It is still not well understood why there is such a sex predilection for the disease."), Ex. A36. *See also* Biousse, et al., *Update on the Pathophysiology and Management of Idiopathic Intracranial Hypertension*, 83 J. Neurol. Neurosug. Psychiatry 488-494, 488 (2012) ("The exact relationship between obesity and IIH remains poorly understood . . ."), Ex. A32.

[6] Chen et al., *Sex Disparities in Neuro-Ophthalmic Disorders*, 40 Current Eye Res. 247, 248 (2015) ("[S]ex hormones are playing a role in the patho-physiology of the disease. In addition, sex hormones can be modulated by adipose tissue and obesity, which makes alterations in hormones a plausible disease mechanism. However, the mechanism remains largely unknown and studies of hormonal differences in IIH have been inconclusive."), Ex. 38.

[7] *Chen & Wall* at 6 ("It has been suggested that elevated levels of vitamin A may cause overstimulation of RAR a-receptors in the central nervous system, resulting in increased intracranial pressure by impairing CSF absorption."), Ex. A36; Andrews et al., *Idiopathic Intracranial Hypertension and Obesity*, 81 Horm. Res. Paediatr. 217, 219 (2014) (describing the metabolic pathway by which mineralocorticoid receptor activation could plausibly explain the development of PTC among many different patients, including men and children), Ex. A35.

between Levonorgestrel and PTC/IH.

The evidence of a causal association between levonorgestrel and PTC/IH actually begins not with the scientific literature, but with an FDA label change for the levonorgestrel-releasing Norplant contraceptive in the early 1990's. Developed by an organization called the Population Council Inc., Norplant was manufactured by Lerias OY (now Bayer OY) but sold in the United States by Wyeth Pharmaceuticals-- while Leiras OY sold Norplant to the rest of the world. Likewise, Mirena was developed by the Population Council Inc., manufactured by Leiras OY (now Bayer OY) and sold by Berlex Laboratories (now Bayer).

Before any case reports, case series, or other data were published, Wyeth and the FDA began discussions to change the Norplant label to include a PTC/IH warning on the product labeling. Letter to FDA (February 12, 1993) (noting that discussions began as early as November 16, 1992), Ex. D2. According to the plain language of the warning which was ultimately adopted, the change was based solely upon spontaneous case reports. Norplant Label p. 3 (1993) ("There have been reports of idiopathic intracranial hypertension in NORPLANT SYSTEM users"), Ex. D1. The scientific literature did not report any cases until seven months later.[8] Critically, the only criticisms of these publications are Letters to the Editor authored by spokespersons for 1) Wyeth and 2) the group that developed Norplant, and later, Mirena.[9]

After these publications, and after the warning was added to Norplant's label, several

[8] Sunku et al., *Benign Intracranial Hypertension Associated with Levonorgestrel Implants*, P218 (Oct. 19, 1993), Ex. A6. Although later publications also reported cases of PTC both from observations in a clinical setting and based on spontaneous reports, no epidemiological evidence was ever generated. *See* Alder & Fraunfelder, *Levonorgestrel Implants and Intracranial Hypertension*, 332 NEJM 1720 (1995), Ex. A7; Wysowski & Green, *Serious Adverse Events in Norplant Users Reported to the Food and Drug Administration's MedWatch Spontaneous Reporting System*, 85 Obstet. & Gynecol. 538 (1995), Ex. A11.

[9] *See* Weber et al., *To the Editor*, 332 NEJM 1721 (1995) (Wyeth spokespersons), Ex. A10; Sivin, *To the Editor*, 86 Obstet. & Gynecol. 318-9 (1995) (Population Council Inc. scientist involved with Norplant), Ex. A9.

publications reported an association between levonorgestrel and PTC/IH.[10] For example, Bayer's consulting expert, Deborah Friedman, has written that "[i]nvestigating for a secondary cause [of PTC] includes questioning the patient about medication usage", and refers to a list of medications containing, among other things, levonorgestrel implants. *Friedman,* at 30 (2005), Ex. A20. Based upon the Norplant literature, Dr. Bruce and Dr. Newman, two of Bayer's testifying neuro-ophthalmologists, have written that an association exists.[11] On this, Dr. Fraunfelder and Bayer's experts agree-- Dr. Fraunfelder's book, Drug-Induced Ocular Side Effects, has included a section on levonorgestrel and PTC/IH for many years.[12]

b. Reports for Mirena Supporting the Its Role in Causing PTC.

Norplant was removed from the US market in 2002, leaving Mirena as the only long-acting, reversible levonorgestrel-releasing contraceptive available in the US from 2002 to 2013 (when Bayer's Skyla, a lower dose LNG-releasing IUD, entered the market).[13] During this time, a drumbeat of increasing evidence similar to that seen with Norplant was reported to Bayer in the form of spontaneous adverse event reports. These resulted in five different company safety signal assessments.[14] Although the earliest company assessments resulted in the same conclusion as Wyeth's (to remove Mirena when PTC/IH occurs), there was no label change.

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[10] The Norplant experience provides a reliable piece of the total body of evidence upon which experts can rely. "In a toxic substance case in which cause in fact is disputed, an epidemiologic study of the same agent to which the plaintiff was exposed that examined the association with the same disease from which the plaintiff suffers would undoubtedly have sufficient 'fit' to be a part of the basis of an expert's opinion." *Reference Manual on Scientific Evidence* 610-11 n.185 (3d ed. 2011) (emphasis added), Ex. A31. The simple fact that Norplant generally released LNG at a higher rate than Mirena says nothing about the range of actual exposure to drug. As described in detail by Dr. Maggio, serum LNG is actually quite similar between Mirena and Norplant users. Maggio Rpt. At 30-31, Ex. J1. Furthermore, Bayer's scientists and other employees have noted the comparable serum levels and delivery mechanisms of Mirena and Norplant/Jadelle. MIR_PSEU_00080668, Ex. B11; MIR_BB_00088420, Ex. B6.

[11] Biousse et al., *Update on the pathophysiology and management of idiopathic intracranial hypertension*, 83 J. Neurol. Neurosurg. Psychiatry 488, 489 (2012) (Dr. Bruce and Dr. Newman listed as co-authors) (listing LNG as a precipitant of IIH, among other drugs), Ex. A32.

[12] Fraunfelder et al., Drug Induced Ocular Side Effects 7th ed., 201 (2015) (citing the Norplant articles), Ex.A9.

[13] Mirena was first marketed in the United States in 2001, having been approved by the FDA in late 2000.

[14] *See* 2001 Signal Assessment, Ex. B1; 2006 Signal Assessment, Ex. B2; 2008 Signal Assessment, Ex. B3; 2014 Signal Assessment, Ex. B4; 2015 Signal Assessment, Ex. B5. Bayer has complained that the 2001 and 2006 assessments are not truly "signal assessments", yet they meet Bayer's own definition of signal assessment according to its Standard Operating Procedures, p. 2, Ex. B11.

In mid-2006, Berlex (which originally marketed Mirena, and was the US subsidiary of Schering), was acquired by Bayer. As seen in Bayer's 2008 signal assessment, the change in management also signaled a significant change in the manner by which signal assessments were handled and the information conveyed to physicians who asked the company about a potential causal association. Now, Bayer sought "confirmed evidence for a causal association" and carefully scrutinized spontaneous reports in order to justify its pre-determined conclusion that no association existed.[15] Rather than advising physicians to consider removing Mirena as Berlex had done, Bayer simply told inquiring doctors that no association existed.

Notably, due to mandatory reporting requirements, the spontaneous reports upon which Bayer's signal assessments are based are essentially the same spontaneous adverse event reports that are in the WHO's spontaneous reporting database (reviewed by Dr. Fraunfelder), as well as in the FDA Adverse Event Reporting System ("FAERS") (reviewed by Dr. Ross). *See* Plouffe Dep. 115:17-117:17 (Bayer did not search the FAERS data until 2015, but according to Dr. Plouffe, "if you look at the end result, we had the vast majority of cases."), Ex. L1. **Thus, the same evidentiary sources that Bayer used to *refute* a causal connection (literature reviews, case reports, and spontaneous adverse event reports) in its safety signal investigations are the same pieces of evidence that it now claims are not reliable enough for Plaintiff's experts to engage in a similar analysis.** Such a position is plainly nonsensical.

c. Epidemiological Evidence Proving Mirena's Causation of PTC/IH.

Following the majority of these internal safety assessments, two epidemiological studies entered the scientific literature in 2015, one proving and the other suggesting a causal association between Mirena and PTC/IH. The first is the Rai/Digre study discussed above. The study and

[15] 2008 Signal Assess., MIR_INDNDA-00246312, Ex. B3; 2014 Signal Assess. p. 7, MIR_PKEU_00699327, Ex. B4; 2015 Signal Assess. p. 1, MIR_KCOPLEY_JSEU_00000024, Ex. B5.

its results were presented at the annual meetings of two prominent organizations: the Association for Research in Vision and Ophthalmology ("ARVO") and the North American Neuro-Ophthalmology Society ("NANOS").[16] The study abstract was ultimately published in one of the ARVO journals. The Rai/Digre study found that there is an odds ratio of 7.7 that Mirena users will develop PTC/IH. *Rai/Digre* at 1, Ex. A42. These results are statistically significant, because the confidence intervals are both greater than 1, with a very small p-value. *Id.* (finding 95% confidence intervals of 3.2-16.4, and $p<0.001$).[17] As the authors of one study upon which Bayer relies have stated, very small p-values are evidence of likely causation.[18]

This Rai/Digre data came from a group of 59 PTC/IH patients seen at the Moran Eye Center from 2008-2013 who were female, 18 years of age or older, who had no known causative etiology for their PTC/IH, and who agreed to provide a telephone birth control history. *Valenzuela/Digre* at 2, Ex. A44.[19] Eight of the 59 patients were on Mirena within 3 months of onset of symptoms, and developed symptoms while the Mirena was in place. *Valenzuela/Digre* at 2, Ex. A44. Any differences in Mirena users and non-users were not statistically significant. *Id.* Thus, the study was comprised of 8 cases (women who used Mirena

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[16] Rai/Digre et al., *The relationship between the levonorgestrel-releasing intrauterine system and idiopathic intracranial hypertension*, ARVO 2015 Annual Meeting Abstracts #278 (2015), Ex. A42; Valenzuela/Digre et al., *Exploratory Study of the Relationship between the Levonorgestrel-Releasing Intrauterine System and Idiopathic Intracranial Hypertension*, North American Neuro-Ophthalmology Society 41st Annual Meeting P102 (2015), Ex. A44.

[17] Reference Manual for Scientific Evidence 3d, p. 577, 621 (2011) ("The most common [p-value,] used in science is .05. A .05 value means that the probability is 5% of observing an association at least as large as that found in the study when in truth there is no association.") ("Where the confidence interval contains a relative risk of 1.0, the results of the study are not statistically significant."), Ex. A31.

[18] Giuseffi et al., *Symptoms and disease associations in idiopathic intracranial hypertension (pseudotumor cerebri): A case-control study*, 41 Neurology 239, 241 (1991) ("Strong associations between IIH and obesity ($p < 0.00001$) and weight gain during the 12 months before diagnosis ($p < 0.0001$) support the conclusions of Digre et al., and Ireland et al. [that these are causes of PTC.]"), Ex. A3.

[19] Presumably, these data were gathered from the same databases identified in Passi et al., who are from the same research group as Rai/Digre study, who published a similar abstract on incidence of PTC among tetracycline users at the same meeting as Valenzuela/Digre et al., and who identified the databases. Passi et al., *Incidence of Idiopathic Intracranial Hypertension (IIH) Among Users of Tetracycline Antibiotics*, North American Neuro-Ophthalmology Society 41st Annual Meeting P106 (2015), Ex. A41.

when they developed PTC/IH), and 51 controls (women who were not using Mirena when they developed PTC/IH). *Id.* Statistical power for the study was generated by then comparing these cases and controls with cohorts of Mirena users and non-users drawn from a population of approximately 220,000 women. *Rai/Digre* at 1, Ex. 42. In this way, the Rai/Digre study was completed in a manner consistent with, if not more scientifically sound than, the "general incidence" epidemiological studies on PTC/IH, outlined above. *See* note 3, *supra*.

The second study was a two-pronged epidemiological study that purported to evaluate the risk of intracranial hypertension with Mirena, conducted by Etminan et al. The first prong of the study involved a disproportionality analysis of reporting PTC/IH among Mirena users in the FAERS database.[20] The second prong of the study compared the risk of developing PTC/IH to oral, combined estrogen-progestin contraceptives (a much different analysis than the Rai/Digre study), and found that there was increased reporting of PTC/IH and papilledema with odds ratios of 1.78 and 1.50, respectively. *Id.* at 110. The comparative risk between Mirena and the combined oral contraceptives did not yield statistically significant results, because the confidence intervals included 1. *Id.* As discussed further below, the Etminan study is therefore of limited utility for purposes of Plaintiffs' claims and Bayer's defenses.

ARGUMENT

I. Plaintiff's Experts Are Clearly Qualified to Offer Their Expert Opinions.

A. Drs. Ross, Fraunfelder, Tang and Maggio Are Qualified to Give General Causation Opinions.

Plaintiff's experts are immensely qualified. As discussed in detail above, each has significant education, expertise, training, and experience to offer their opinions. Unlike many of

[20] Etminan et al., *Risk of intracranial hypertension with intrauterine levonorgestrel*, 6 Ther. Adv. in Drug Saf. 110 (2015), Ex. A47.

Bayer's expert witnesses, Plaintiffs' experts are not professional witnesses. They are treaters, teachers, and research scientists. Nevertheless, Bayer contends that Plaintiff's experts are somehow unqualified to give opinions on general causation, specific causation and/or any information conveyed to doctors and patients about the dangers of a prescribed product.

Bayer supports its argument with case cites from around the United States, but not one case from this circuit. This is likely because the Eighth Circuit considers Rule 702 to be a liberal standard of admissibility. *See, e.g., Johnson v. Mead Johnson & Co., LLC*, 754 F.3d 557, 558 (8th Cir. 2014) ("cases are legion that, correctly, under *Daubert*, call for the liberal admission of expert testimony.")

Expert testimony is presumed to be helpful unless it concerns matters within the everyday knowledge and experience of a lay juror. *See United States v. Shedlock*, 62 F.3d 214, 219 (8th Cir. 1995). "[T]the fit between an expert's specialized knowledge and experience and the issues before the court need not be exact[.]" *Travelers Prop. Cas. Co. of Am. v. Nat'l Union Ins. Co. of Pittsburgh*, 557 F. Supp. 2d 1040, 1051 (W.D. Mo. 2008). Plaintiff's experts have the education and training that qualify them to offer the jury assistance. Regulatory specialist Dr. Ross has an extensive background with the FDA, Dr. Fraunfelder is an ophthalmologist with experience and expertise as a medical doctor and in drug safety monitoring and ocular side effects, Dr. Maggio is a pharmacologist and research scientist, and Dr. Tang is a neuro-ophthalmologist treating patients with PTC/IH.

Here, Plaintiff's experts engaged in a literature review, including the review of the epidemiology studies involving both the general incidence of PTC/IH and the specific epidemiology studies indicating that the Mirena is significantly associated with the development of PTC/IH. Under *Daubert*, "[t]here is no requirement 'that a medical expert must always cite

published studies on general causation in order to reliably conclude that a particular object caused a particular illness. […] Even if the judge believes there are better grounds for some alternative conclusion, and that there are some flaws in the scientist's methods, if there are good grounds for the expert's conclusion, it should be admitted[.]" *Bonner v. Isp Techs.*, 259 F.3d 924, 929 (8th Cir. 2001) (internal citation omitted).

Bayer further alleges that the Plaintiffs' experts are not qualified to testify as to causation because they were not trained as epidemiologists. However, this position has been rejected by many, many courts, including those in the Eighth Circuit. *See, e.g., Kennedy v. Collagen Corp.*, 161 F.3d 1226 (9th Cir. 1998) (physician is permitted to testify about causation); *DeLuca v. Merrell Dow Pharms., Inc.*, 911 F.2d 941, 953 (3d Cir. 1990) (pediatric pharmacologist expert's credentials are sufficient pursuant to Fed. R. Evid. 702 to interpret epidemiologic studies and render an opinion based thereon); *Medalen v. Tiger Drylac U.S.A., Inc.*, 269 F. Supp. 2d 1118, 1129 (D. Minn. 2003) (holding toxicologist could testify to general causation but not specific causation); *Trach v. Fellin*, 817 A.2d 1102, 1117–18 (Pa. Super. Ct. 2003) (an expert who was a toxicologist and pathologist was permitted to testify to general and specific causation). The idea that doctors and pharmacologists cannot opine on epidemiology, which they have been trained to use every day, is simply absurd. Indeed, Bayer has insisted upon the absurdity of this argument in defense of its own experts in related actions, despite the fact that Plaintiffs have not even argued for exclusion on these grounds in their opening briefs. *See* Appx. A ("Medical doctors do not need to be epidemiologists in order to testify regarding epidemiological studies.") Bayer cannot have it both ways.

B. Medical Doctors and Pharmacologists Are Qualified to Opine on the Sufficiency of a Label.

Bayer alleges that Plaintiff's experts are not qualified to opine that Mirena's label is

inadequate from a regulatory perspective because they have no prior regulatory experience.[21] Bayer cites *Wehling v. Sandoz Pharms. Corp*., No. 97-2212, 1998 WL 546097 at *4 (4th Cir. Aug. 20, 1998) as support for that contention. However, in disqualifying an expert in that case, the *Sandoz* court noted that the proposed expert was **neither a pharmacologist nor a medical doctor**; presumably, had he been either, this would have qualified him to opine on label warnings. In this case, Dr. Maggio is a pharmacologist (who teaches medical students *about the pharmacology of the drugs they will prescribe*) and Dr. Ross, Dr. Fraunfelder and Dr. Tang are practicing physicians who each prescribe drugs every day. Thus, all three are qualified to explain the need for warning labels to notify prescribers of concerns regarding the potential dangerous adverse effects of a particular drug. Moreover, Dr. Tang's clinical and research background specifically includes experience with patients that developed PTC/IH while using a levonorgestrel-releasing contraceptive system. *See* Tang Report at 5, Ex. N1. The sheer number of expert neuro-ophthalmologists disclosed by Bayer (four) to dispute Dr. Tang's opinions speaks to the highly relevant clinical implications of drug-induced PTC/IH, far beyond a gynecologist's initial prescribing decision. In addition to affecting the prescribing decisions of doctors, and the patients choice to use a particular contraceptive, drug warnings affect how practicing physicians like Dr. Tang evaluate patients in a clinical setting, and determine a patient-specific course of treatment. Tang Rpt. at 7, 8 ("This type of information would be helpful to . . . healthcare providers who see patients, while on this medication, who may be experiencing symptoms that may be related to increased intracranial pressure"), Ex. N1.

As discussed above, Rule 702 is a liberal standard of admissibility. Lack of direct

[21] Bayer's first "issue presented" also frames the issue in a very misleading manner. As described herein, Plaintiffs' experts certainly ***do have*** significant experience, education, training, and expertise in PTC/IH, epidemiology, and the FDA regulatory regime. As explained in Plaintiff's Suggs. in Supp. of Mot. to Exclude Expert OB/GYNs, DN 75, gynecological experience is actually irrelevant to these cases because Mirena has never had a warning for PTC/IH.

experience is not a sufficient basis to reject the proposed testimony; it affects the weight of the testimony is given by the jury. *See Parker v. Allentown, Inc.*, 891 F. Supp. 2d 773, 785 (D. Md. 2012) ("Moreover, 'the fit between an expert's specialized knowledge and experience does not need to be exact'"). Plaintiffs' experts have the education and training that qualify them to offer the jury assistance in deciding the technical issues in this case; Bayer's motion should be denied.

II. Bayer's Criticisms of the Evidence Supporting a Causal Association Are Unfounded.

First, Bayer's contention that Plaintiff's experts cannot prove causation because "by definition idiopathic intracranial hypertension has no known cause" cannot be taken seriously. [DN 66] at 2. Each of Bayer's disclosed expert neuro-ophthalmologists has contributed to peer-reviewed literature establishing levonorgestrel among secondary causes, or medication-induced variations of PTC/IH.[22] Bayer conveniently ignores these and other publications by its own retained experts characterizing "Secondary Intracranial Hypertension", "Medication Associated Intracranial Hypertension" and "Medication-Induced Intracranial Hypertension" in an attempt to confuse and mislead the Court. Such an argument is, and should be, easily discarded as disingenuous and pedantic.

A. The Rai/Digre Study is a Reliable Basis for the Opinion that Mirena is Causally Associated with PTC/IH.

The Rai/Digre abstract is a reliable basis for Plaintiff's experts to conclude that general causation exists. First, the odds ratio of 7.7 determined from the Rai study is well in excess of the threshold amount of 2.0 needed in order to determine general causation from an

[22] *See* Deborah Friedman, *Medication-Induced Intracranial Hypertension in Dermatology*, 6 Am. J. Clin. Dermatol. 29, 30 (2005), Ex. A20; Deborah Friedman, *Idiopathic Intracranial Hypertension*, 11 Current Pain and Headache Reports 62, 67 (2007), Ex. A26; Biousse et al., *Update on the pathophysiology and management of idiopathic intracranial hypertension*, 83 J Neurol Neurosurg Psychiatry 488, 489 (2012) (Bruce, Newman co-authors), Ex. ___; Gans et al., *Idiopathic Intracranial Hypertension Treatment & Management*, Medscape (2016) (Chief Editor Lee), Ex. A32; Deborah Friedman, *Papilledema*, Ch. 5 in Walsh & Hoyt's Clinical Neuro-Ophthalmology 237 (2006) (Newman, ed.), Ex. 24.

epidemiological study. *Rai/Digre* at 1, Ex. A42. "Some courts have insisted on a doubling of disease as a minimum for proof of specific causation, while others have recognized that, if other known causes can be identified and eliminated, something less than a doubling would still support finding specific causation." *See* Restatement (Third) of Torts: Liability for Physical and Emotional Harm § 28 cmt. c(4) rptrs. note (2010). Standards of reliability need not be so high as to keep out ***all*** evidence; any alleged flaws go to the credibility afforded to experts, after traditional cross examination.

Because Rai/Digre so strongly supports an inference of causation (exceeding the threshold required in some jurisdictions by more than three times), Bayer uses a parade of horribles to attempt to undermine the study, but none of these concerns are based in reality. First, and most misleadingly, Bayer argues that the results of Rai/Digre are confounded by not controlling for BMI. However, Bayer wholly fails to show 1) that the rates of obesity between Mirena users and other women of childbearing age are enough to actually confound the results (if they are different at all), and 2) ignores Plaintiff's success in demonstrating with Bayer's own expert that even under a worst-case scenario, the Rai/Digre results are only minimally impacted, going no lower than an odds ratio of 5.7, as explained below. Further, so long as the underlying data were generated to a 95% certainty, they are reliable. *See In re Viagra Prods. Liab. Litig.*, 572 F. Supp. 2d 1071, 1078 (D. Minn. 2008) (citing *Reference Manual* at 389) (odds ratio provides reliable evidence of causation when generally accepted confidence intervals of 95% are used).

Only two studies have evaluated rates of use of Mirena among women of various body-mass indexes ("BMI"): A Hawaiian study by Saito-Tom et al., and a study by Pleipert et al.

based out of Missouri.[23] None of Bayer's experts have cited to either of them. As demonstrated during Dr. Langer's (a Bayer expert) deposition, when adjusting the 7.7 Rai/Digre odds ratio based on the "preferential prescribing" in the Saito-Tom article, and the risk ratios Dr. Langer described from Daniels 2007, reduces Rai/Digre's odds ratio no further than a 5.7 –still almost three times the universally accepted legal standard for causation. *See* Langer Depo 166:17-18, Ex. H2; *see generally id.* at 156:19-171:14 (adjusting Rai OR); Langer Deposition Exhibits 14-16 (spreadsheets showing adjustments), Exhibit H3. Even when adjusting based on Dr. Langer's suggested criteria, that 85% of Mirena users are morbidly obese, he was forced to admit that the results remained statistically significant— ***a fact that Dr. Langer had previously investigated but omitted from his report.*** Langer Depo 171:15-174:9, Ex. H2. This is in line with the results seen in Pleipert et al., who did not find it necessary to adjust their results for BMI: "[…B]ody mass index (BMI) [and other potential confounders] were assessed, but none of these variables made a significant (> 10%) change on the effect estimate. Thus, we present unadjusted hazard rate ratios and relative risks." Pleipert et al. at *5, Ex. 48

Rather than confronting actual data on preferential prescribing (or lack thereof), Bayer instead seeks to distract this Court with various "guidances" published by the CDC, Mayo Clinic, and the American College of Obstetrics and Gynecology to generate an inference that Mirena *may* be preferentially prescribed to obese women, thus confounding the Rai/Digre results. *See* Bruce Report p. 16, Ex. E1; Langer Report p. 5-6, Ex. H1; Newman Report p. 7, Ex. K1. However, the ACOG bulletin supporting their contention was recently withdrawn; indeed, it was actually withdrawn before Bayer's experts all submitted their reports unanimously citing to it. *See* List of Withdrawn ACOG Bulletins, Ex. A21. Moreover, most of the "guidances" upon

[23] Saito-Tom et al., *Levonorgestrel Intrauterine Device Use in Overweight and Obese Women*, 74 Hawai'i J. Med. & Pub. Health 369 (2015), Ex. A43; Peipert et al., *Continuation and Satisfaction of Reversible Contraception*, 117 Obstet. & Gynecol. 1105 (2011), Ex. A49.

which Bayer relies actually recommend long-acting reversible contraceptives generally, including non-hormonal types.[24] They do not specifically recommend Mirena.

Finally, it is important to note that Dr. Saito-Tom's article was based on studies of a Hawaiian population of Mirena users. Comparison between the population studied there and the population of the United States at large shows that Dr. Saito-Tom's study is not reflective of the demographics of the United States overall, either with respect to rates of obesity and overweight, or with respect to racial make-up. If anything, higher rates of obesity and overweight in the rest of the United States make it less likely that Mirena is actually preferentially prescribed to overweight or obese women.[25] In studying Midwestern women, Pleipert et al. did not deem it necessary to adjust for BMI.

Scientific research need not be published or peer reviewed to be considered a reliable basis of expert opinion in this Court. *Bonner v. Isp Techs.*, 259 F.3d 924, 929 (8th Cir. 2001) ("There is no requirement that published epidemiological studies supporting an expert's opinion exist in order for the opinion to be admissible.") Nevertheless, the Rai/Digre study results ***were*** published in the Investigative Ophthalmology & Visual Science Journal, published by the prestigious Association for Research in Vision and Ophthalmology ("ARVO") organization.[26] *See* Rai/Digre et al., Ex. 42. Despite being published in Volume 56, Issue 7 at page 2228, and being presented at two prestigious annual conferences, no scientist anywhere in the world (other than one paid by Bayer) has openly criticized the Rai/Digre study, written a letter to the editor to

[24] There are no reported cases of PTC/IH in connection with the use of the Paragard IUD.
[25] *Compare* Saito-Tom at 369, 372 (2015) (study population composed of 78% Asian, Native Hawaiian, or Pacific Islander; 46% of Hawaiian women overweight or obese, nearly 60% of US women overweight or obese), Ex. A43; U.S. Census Bureau, *QuickFacts: United States* (Sept. 15, 2016) (only 5.8% of Americans are Asian, Native Hawaiian or Pacific Islander), *available at* https://www.census.gov/quickfacts/table/PST045215/00, Ex. A46.
[26] "ARVO is the largest and most respected eye and vision research organization in the world. Our members include nearly 12,000 researchers from over 75 countries."
http://www.arvo.org/About_ARVO/Who_We_Are/ Indeed, even Bayer's neuro-ophthalmology experts belong to ARVO, attend its conferences, and otherwise have participated in the organization's activities.

criticize it, or replicated the study and achieved different results. What we do know is that Bayer's non-testifying consulting witness (Dr. Deborah Friedman) has "reached out" to the study's authors for some unexplained reason; perhaps to influence future publishable results.

Bayer also criticizes the Rai/Digre study because the data sources are allegedly unknown. First, this is not correct, because the authors (part of a neuro-ophthalmology research group practicing out of the University of Utah, which is known to have a registry for IIH patients), state in the NANOS abstract that their cases come from their own PTC/IH patients. *Valenzuela/Digre* at 2, Ex. A44. This is really no different from any other epidemiological studies done on PTC/IH, *see* "Facts" § 3.a, *supra*. Furthermore, an abstract from the same group, published at the same time as the NANOS abstract, indicates the likely databases for the cases, controls, and cohorts for the Rai/Digre study.[27] Bayer also offers no reason why the health claims database used should be less reliable than any other health claims database. Despite being the manufacturer of a multi-billion dollar product "significantly associated" with PTC/IH, Bayer has conducted no studies of its own to show that these results are actually unreliable.

There is no reason to believe that incorrect ICD-9 or CPT codes were used, as Bayer claims. With respect to the numerator: again, the Rai/Digre authors gathered their cases and controls from among their patients; therefore, their diagnoses were confirmed. *See Valenzuela/Digre* at 1, Ex. A44. Regarding the denominator: the Rai/Digre study states that cohort members with "pseudotumor cerebri" ICD-9 codes were excluded from the denominator—apparently to prevent double-counting. *See Rai/Digre*, Ex. A42. Pseudotumor cerebri is listed in the index of ICD-9 and assigned a single code, 348.2. ICD-9 Code & Index,

[27] Passi et al., *Incidence of Idiopathic Intracranial Hypertension (IIH) Among Users of Tetracycline Antibiotics*, North American Neuro-Ophthalmology Society 41st Annual Meeting #106 (poster) (2015) (using the RedCap IIH database and FURTHeR database which contains the "University of Utah Enterprise Data Warehouse (a database of all individuals seen at University of Utah hospitals and clinics)"), Ex. A41.

Ex. C2; there is simply no reason to be concerned that exclusion of cases from the 220,000 woman cohort in the denominator by this code would be inaccurate. Even if it were, the difference the 59 cases of PTC/IH excluded from the cohorts of a total of 220,000 would have an extremely minimal impact on the results. Bayer's criticisms of the failure to survey the Rai/Digre cohorts therefore are also unfounded. Notably, comparator groups used in other "general incidence" epidemiological studies (for instance, the Daniels 2007 quality of life comparators) did not have their medical records checked for accuracy. In addition, based on Passi et al., it seems the CPT codes likely came from the medical records themselves, Ex. A41.

Bayer criticizes the method of collecting cases for the Rai/Digre study, completely ignoring the fact that the epidemiological studies Bayer relies on for general incidence rates have essentially the same methodology.[28] Based on Valenzuela/Digre's statement under "Methods", it is clear that medical records and personal contact information was available to the University of Utah group. *Valenzuela/Digre* at 1, Ex. A44. This is certainly evidence that the cases and controls were identified in a similar fashion to other PTC/IH general incidence epidemiology studies. Bayer does not explain why methods their experts consider reliable for general incidence studies should be any less reliable when used by the Rai/Digre authors.

Bayer also claims uncertainties in what types of IUDs were used in the Rai/Digre study, and whether PTC/IH diagnoses were accurate in the cohort. Firstly, the Rai/Digre study looked at insertions of LNG-IUS from 2008 to 2013; therefore, the vast majority if not all insertions must be for Mirena because the only other LNG IUD products did not enter the market until late in, or

[28] *See* Durcan et al., *The Incidence of Pseudotumor Cerebri Population Studies in Iowa and Louisiana*, 45 Arch. Neurol. 875, 875 (1988) (using postcards sent to doctors to identify cases), Ex. A1; Radhakrishnan et al., *Epidemiology of idiopathic intracranial hypertension: a prospective and case-control study*, 116 J. Neurol. Sci. 18, 19-20 (1993) (identifying 40 cases from ophthalmology and neurology), Ex. A5; Radhakrishnan et al., *Idiopathic Intracranial Hypertension (Pseudotumor Cerebri): Descriptive Epidemiology in Rochester, Minn, 1976 to 1990*, 50 Arch. Neurol. 78, 78-79 (1993) (identifying 9 cases from a medical records index at Mayo Clinic) Ex. A4; Daniels et al., *Profiles of Obesity, Weight Gain, and Quality of Life in Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)*, Am. J. Ophthal. (2007) (34 IIH patients of 7 researchers identified as cases), Ex. A25.

later than, that time period. *See* Drugs@FDA Liletta and Skyla Approval Dates, Ex. P1-2. To the extent that the CPT codes are not specific enough, as they are for IUD insertion and not specifically LNG-IUS insertion, CPT Code 58300, Ex. C1, this serves only to inflate the denominator of the LNG-IUS cohort with Paragard users. Thus, the danger is that the Rai/Digre odds ratio is actually too low, not too high.

Bayer also complains that the cohorts used in the Rai/Digre study could somehow be different enough from the PTC/IH cases and controls that it would flaw the results. However, we do know from the Valenzuela/Digre abstract that the PTC/IH cases and controls were all seen for PTC/IH and all female, between the dates of 2008 to 2013. *Valenzuela/Digre* at 2, Ex. A44. These groups were not significantly different based on a number of demographic parameters, including BMI. *Id.* Rai/Digre states that the cohorts were limited to women of childbearing age for the same time period. As described above, discrepancies in BMI between the cases and controls versus the cohorts are not actually a serious concern. Therefore, these alleged "differences" seem to be a wholly illusory problem.

Finally, Bayer's contention that the Rai/Digre authors did not find causation is misleading. Clearly, the authors found there was cause for concern, because they recommend augmenting evaluation of PTC/IH patients with a birth control history. Rai/Digre at 1, Ex. A42 ("we recommend augmenting the routine evaluation of IIH with a birth control history"). Even if the authors claim that a causative role for Mirena has not yet been established, there is no evidence that Rai/Digre reach this conclusion based on a preponderance of the evidence—rather, they are speaking as scientists. Thus, the authors' conclusions certainly do not rule out a causative role (more likely than not) for Mirena, nor diminish the reliability of their study.

Generally, in order for a fact to be considered "true", scientists require 95%

certainty. Even Bayer's own experts agree with this principle. Langer Dep. 78:9-17, Ex. H2. This is best exemplified by the use of 95% confidence intervals (showing that the true value is within a range which is 95% certain to be true) and 0.05 p-values (indicating a 95% certainty that the results are not due to chance). *Id.* As a result, scientists are frequently hesitant to make claims which cannot be so quantified, but prefer to state conclusions in terms of associations. Legal scholars have identified this fact as creating a problematic disconnect between the scientific world (where certainty can only rarely be declared), and the legal world.[29] Failure to state causation in scientific literature-- which is held to a scientific burden of proof of 95%-- should not be taken literally in a civil case, where the burden of proof is less.[30]

In sum, Bayer's critiques are wholly unfounded. A perfect study that complies with all of Bayer's requirements probably does not exist anywhere and would have been impossible to perform. This is exactly why Rule 702 and *Daubert* permit experts to rely upon statistical data that is not perfect—it need only be reliable and trustworthy. Reliability may be established by showing that the opinion, or evidence underlying it, meets a non-exclusive list of factors or shows other indicia of reliability. Here, the Rai/Digre results are testable and there are enough of their methods described here to be verifiable. Bayer need only attempt a similar study to see if these results are in fact reproducible, but has chosen not to do so. The Rai/Digre study is also reliable and trustworthy because it was completed by a completely independent third party,

[29] See Danielle Conway-Jones, *Factual Causation in Toxic Tort Litigation: A Philosophical View of Proof and Certainty in Uncertain Disciplines*, 35 U. Rich. L. Rev. 875, 917-940 (2002) (detailing the interplay and differences between burdens of proof in civil litigation and science), Ex. A17.

[30] The Reference Manual on Scientific Evidence notes that some courts have been confused by the need for confidence intervals of 95% to demonstrate statistical significance with the ultimate burden of proof, requiring therefore a confidence interval of only >50%, or a p value of <0.5. Ref. Man. Sci. Evid. 3d at 577 n. 81, Ex. A31. Plaintiffs do not disagree that 95% confidence intervals and p values <0.05 are certainly indicia of reliability for any study (Rai/Digre generated 95% confidence intervals of 3.2-16.4, p value <0.01, for example) —but neither are they a prerequisite. Further, Plaintiffs maintain that ultimate conclusions are distinct from confidence intervals: while scientists generally prefer to state certainties in terms of 95% in *all* matters, ultimate conclusions regarding causation cannot be held to this high standard in a civil case.

affiliated with neither Plaintiff nor Bayer. Accordingly, Bayer's motion should be denied.

B. The Etminan Article is But One Piece of the Totality of the Evidence in Supporting a Causal Association Between Mirena and PTC/IH.

Bayer argues that the Etminan article is largely unreliable, making much of the fact that it found no statistically significant difference between the risk of developing PTC/IH with Mirena and oral contraceptives. First, Mirena is not an oral contraceptive. Second, for some reason, Etminan's study compared Mirena against two specific oral contraceptives (EE-norgestimate and EE-norethindrone) out of many different oral contraceptives. Norgestimate-Ethinyl Estradiol is a *combination* of a progestin (norgestimate) and an estrogen (ethinyl estradiol). Likewise, Norethindrone-Ethinyl Estradiol is a *combination* of a progestin (norethindrone) and an estrogen (ethinyl estradiol). Mirena, on the other hand, is composed of a single, potent, synthetic progestin (levonorgestrel): it contains no estrogen. In this case, Plaintiff has never claimed that the Mirena is more or less dangerous than these two oral, combination contraceptive products. Therefore, Etminan's "retrospective cohort study" (as opposed to his disproportionality analysis) comparing the risk of developing PTC/IH between levonorgestrel (a progestin) with two oral, combined contraceptives (a progestin combined with an estrogen) is of limited, if any, relevance to Plaintiff's case theories. Nor is it of any particular relevance to Bayer's defenses.

Regarding Etminan's disproportionality analysis of the FDA FAERS database, Plaintiff also has criticisms of Etminan's work but Plaintiff (like Bayer) had no control over Etminan's research questions, research methods, results or publication. For instance, Plaintiff believes that Etminan's search terms were underinclusive, not overinclusive. Moreover, Etminan's article is not clear whether his disproportionality analysis compared Mirena to *all* drugs in the FAERS database (as it should have) or whether it compared Mirena only to the combination oral contraceptives evaluated in his restrospective cohort study. Additionally, Etminan's "prior

distribution" rate for the general incidence of PTC/IH is grossly inflated from even the literature to which he cites for his 10-20/100,000 rate. In fact, the literature that Etminan cites provides a range of 0.9 to 1.0/100,000 in the general population, 1.6-3.5/100,000 in women, and 7.9-20/100,000 in overweight women. *See* Medscape, *Idiopathic intracranial hypertension* (2014), *at* http://emedicine.medscape.com/article/1214410-overview#a0156. As noted in the source Etminan cites, annual incidence rates compiled by the Mayo Clinic between 1976 and 1990 are much lower than his estimate: a) 0.9 case per 100,000 people; b) 1.6 cases per 100,000 women; c) 3.3 cases per 100,000 females aged 15-44 years; and d) 7.9 cases per 100,000 obese women aged 15-44 years. *See id.* Thus, Etminan's grossly inflated "general incidence" rate actually serves to *minimize* the association between Mirena and PTC/IH.

Additionally, Etminan's disproportionality analysis is tantamount to an apples-to-oranges comparison in one very important respect. A disproportionality analysis is designed to compare drug A (and its corresponding drug-related adverse event reports) to all drugs (and their corresponding drug-related adverse event reports). Etminan, however, failed to recognize that upwards of one quarter to one third of all Mirena adverse event reports were *device-related* reports (i.e., migration of the device, expulsion of the device, perforation of the uterus, insertion-related injuries, etc.). The drugs to which he compared Mirena would have no such device-related adverse event reports. Including these device-related adverse event reports vastly inflates (by up to a third) the denominator of adverse events related to Mirena. If the device-related reports are excluded from the disproportionality analysis, the reporting odds ratio is actually significantly higher than what Etminan found.

While Plaintiff has identified limitations, biases, and deficiencies in Etminan's article, Plaintiff can identify similar limitations, biases and deficiencies in each of the studies cited by

Bayer, including the "general incidence" and "risk factor" epidemiology studies. However, as Bayer's experts readily admit, no study is without limitations, biases and deficiencies. This does not make the studies any more or less reliable (i.e., trustworthy) and practicing physicians rely on the studies nonetheless. Unlike Bayer, which has thousands of doctors at the disposal of the company's research funding arm, Plaintiff has no way to conduct studies, coordinate responses to studies that Plaintiff may not like or agree with, or otherwise participate in the medical peer review process. Instead, litigants are left to contend with perceived limitations, biases, and deficiencies by engaging in effective cross-examination of the experts who rely on such studies.

Additionally, Bayer's argument about oral contraceptives and PTC/IH is irrelevant here, as its experts candidly admit that the studies specifically investigated an association to oral contraceptive use. *Id.* Critically, as Bayer's retained consulting expert Dr. Friedman has explained, "[i]n contrast to oral contraceptives, ***there is a well established relationship between PTC and levonorgestrel-releasing implants.***" Friedman 2005, Ex. A20 (emphasis added). Finally, the evidence for OCs is only minimally applicable to Mirena, because OCs contain an estrogen. That means that the pharmacology of OCs is different from LNG-only contraceptives like Mirena and Norplant, and are not as comparable. *See* Plaintiff's Mem. in Support of Mot. to Excl. Dr. Jusko, DN 77.[31] Further illuminating the inapplicability of these studies, even in medical literature authored by Bayer's own retained, testifying experts, purportedly undermining an association to oral contraceptives, LNG is specifically listed as a

[31] Notably, earlier studies on the risk of developing intracranial hypertension with oral contraceptives have also not yielded statistically significant results.[31] "Where the confidence interval contains a relative risk of 1.0, the results of the study are not statistically significant." Reference Manual on Scientific Evidence 3d, p. 621 (2011) (defining "confidence interval"), Ex. A31. When a study fails to find a statistically significant association, the result may either "tend[] to exonerate the agent's toxicity[,] or is essentially inconclusive with regard to toxicity." Id. at 582. Yet, Bayer's experts rely on these two under-powered studies for their contentions that "epidemiologic and case-control studies have specifically shown a lack of association between the use of oral contraceptives and the development of IIH." See e.g., Newman Rpt. at 5 (citing Digre 1984; Durcan 1988; Ireland 1990; Giuseffi 1991; Radhakrishnan 1993), Ex. K1.

medication associated with PTC/IH distinct from any discussion regarding oral contraceptives.[32] Accordingly, Bayer's motion should be denied.

C. Case Reports and Spontaneous Adverse Event Reports Are Proper Bases of the Totality of Evidence Upon Which Experts May Rely Under Rule 702.

It is perfectly appropriate for case reports and spontaneous reports to form part of the basis of an expert's opinion, particularly where epidemiological evidence also supports causation. Bayer's citations to cases where ***only*** case reports formed the basis of the experts' opinions are easily distinguishable. [DN 66] at 22. For instance, the Eastern District of Missouri in *Glastetter v. Novartis Pharms. Corp.*, did not believe that "case studies ***in this case*** are sufficient ***alone*** to 'establish the requisite causation […]." 107 F. Supp. 2d 1015, 1031 (E.D. Mo. 2000) (emphasis added). The District of South Dakota agreed, finding Defendants' citation to *Glastetter* "not dispositive. *Glastetter* simply states that 'causal attribution based on case studies must be regarded with caution.' Here, [the expert] is not using case studies as the entire foundation for his opinions, but just as one piece of the puzzle." *Berg v. Johnson & Johnson*, 940 F. Supp. 2d 983, 997 (D.S.D. 2013). Likewise, here, strong epidemiological evidence, in addition to other types of evidence, also exists. Spontaneous reports and case reports are not the sole basis for causation here; far from it. The Rai/Digre study ***alone*** is sufficient to prove causation in a civil case. However, spontaneous reports and case reports do form part of the "totality of evidence" that Mirena more likely than not causes or is a substantial factor in causing PTC/IH. Dr. Ross also appropriately considered case reports as additional evidence of breach of duty in failing to change the label. Indeed, the Norplant label was changed almost as soon as it was marketed in the US, due to spontaneous reports.

II. Plaintiffs' Experts Reliably apply the evidence for the causal role of Mirena in

[32] See e.g., Biousse et al., *Update on the pathophysiology and management of idiopathic intracranial hypertension*, 83 J Neurol Neurosurg Psychiatry 488, 489 (2012) (Bruce, Newman co-authors), Ex. A32.

contributing to PTC.

Under *Daubert*, the Eighth Circuit has adonished district courts "not to weigh or assess the correctness of competing expert opinions. As long as the expert's scientific testimony rests upon 'good grounds, based on what is known' it should be tested by the adversary process with competing expert testimony and cross-examination, rather than excluded by the court at the outset. *Johnson v. Mead Johnson & Co., LLC*, 754 F.3d 557, 562 (8th Cir. 2014) (quoting 509 U.S. at 590, 596. Bayer makes numerous spurious claims to suggest that Plaintiff's experts have not reliably applied the evidence in this case. Each of these claims are totally unfounded, not only because the evidence at issue *is* reliable, but also because Plaintiff's experts fairly accounted for and considered weaknesses in that evidence.

A. Dr. Rick Fraunfelder

Dr. Fraunfelder offers reliable general causation opinions. He bases these opinions on "the body of evidence" indicating a causal association between Mirena and IIH. Fraunfelder Dep. 31:18; 144:1-144:2; 153:13-153:20, Ex. G3. In its argument that none of Plaintiff's experts "have ever diagnosed IIH", Bayer concedes that Dr. Fraunfelder (like Dr. Tang) in fact has. [DN 66] at 13. While a lack of such experience would not be proper grounds for exclusion, clearly Bayer finds Dr. Fraunfelder's qualification relevant to his general causation opinions.

First, Bayer argues, without merit, that Dr. Fraunfelder could not remember Dr. Etminan's epidemiological study. [DN 66] at 17. Initially, it bears noting that Bayer's counsel *insisted* Dr. Fraunfelder answer questions regarding Dr. Etminan's methodology, "without re-looking at the article". Fraunfelder Dep. 219:16-219:21, Ex. G3. Dr. Fraunfelder's response, that he hadn't memorized all of the sources included on his materials list, does not make his opinion unreliable. *Id.* at 219:22-219:25. *See Bd. of Trs. of the Aftra Ret. Fund v. JPMorgan Chase Bank, N.A.*, S.D.N.Y., 2011 U.S. Dist. LEXIS 144382, at *39 (Dec. 14, 2011) ("An expert is not

required to have memorized the complete contents of her expert report"). Moreover, Bayer has represented in its *Daubert* responses in related cases – and is expected to do so here – that "[m]emorization of minute details is not a metric for the reliability or helpfulness of an expert's opinion, nor should it be[]", and admonished Plaintiffs' counsel for refusing similar requests of copies to refresh an expert's recollection). *See* Appx. A. Thus, Bayer asks this Court to exclude Dr. Fraunfelder on a basis it finds improper for preclusion of its own experts. This cannot be taken seriously. Furthermore, Bayer's argument that Dr. Fraunfelder "could offer no explanation for his report's speculation that [Etminan's] study might 'suggest a possible class effect[,]'" and that this conclusion is "nonetheless impossible to square with the earlier studies finding no increased risk from oral contractive (*sic*) use" is unpersuasive. [DN 66] at 17. As discussed *supra*, the studies finding no increased risk from oral contraceptive use were insufficiently powered to find a statistically significant result, and did not account for the effect of ethinyl-estradiol (an estrogen, not a progestin) on sex hormone binding globulin.

Regarding the specific details of how the Rai group performed their study, Bayer points to Fraunfelder's suggestion that Bayer depose Dr. Rai, who "might give you the answers you're looking for." Fraunfelder Dep. 188:15–189:1, Ex. G3. Tongue-in-cheek or not, Dr. Fraunfelder expresses the reality that a study's underlying data is frequently not readily available. Indeed, Bayer's counsel has made this point incredibly clear, through its harassing attempts to depose Dr. Etminan about the data underlying his study, despite its profession that *none of Plaintiffs' experts are relying on it.* Yet, again, Bayer is expected to contradict this argument in defense of its own experts. Bayer insists in related cases that its epidemiological experts' reliance on company assessments of data rather than the underlying data itself is *the standard in practice*: "Just as a scientist reviews the data presented in a published study – without reviewing the individual,

patient level data to verify that the summary data is accurately compiled – and determines whether that data supports the conclusions reached, Dr. Bruce should be entitled to review the data presented in Bayer's signal assessment and reach conclusions from it." *See* Appx. A. Additionally, Bayer asserts that Dr. Fraunfelder "opined that the authors meant the opposite of what they said[]", referring to Dr. Fraunfelder's reading that "a causative role has been established in some patients[.]" [DN 66] at 21. Bayer's cherry-picked citation to Dr. Fraunfelder's response is a misrepresentation at best. Dr. Fraunfelder does not, as Bayer suggests, assume the opposite of the authors' conclusions; rather, he explains: "I take it to mean that they don't think it's a direct correlation. It doesn't occur in every case but then the -- the understanding of the conclusion is -- is to understand that taking Mirena doesn't cause [PTC] every time. The meaning is that taking Mirena causes [PTC] more often than if you're not taking it." Fraunfelder Dep. 182:19-183:2, Ex. G3.

Furthermore, Dr. Fraunfelder's basis in "Anecdotal Reports" comes from the "body of case reports, not just one." *Id.* at 144:1-144:2. Regardless, Bayer's criticisms of these reports are largely unfounded and go to the weight, rather than the admissibility of Dr. Fraunfelder's opinions. First, Bayer points to Dr. Fraunfelder's reliance on a 2010 meeting abstract describing a case of "Atypical" IIH. [DN 66] at 24. Bayer's claim that "the case report does not specify that the patient's IUD was a Mirena" is surprising, ***as Mirena, and its foreign equivalents, were the only LNG-IUDs on the market in 2010***. Bayer's citation to the deposition of a withdrawn expert as the only basis for this contention makes clear its lack of foundation. [DN 66] at 24 (citing Etminan Dep. 200:5–8). The assertion that "the patient 'probably' did not meet the criteria for IIH[,]" is similarly flawed coming from Etminan, who is not a medical doctor. *Id.*, citing Etminan Dep. 177:8–13. In fact, the patient's fundus exam revealed "minimum inferior pole

blurring in left optic disc." Martínez et al., *Atypical Pseudotumor Cerebri*, 34 Neuro-Ophthalmology 255, 255 (2010), Ex. A27. As Dr. Fraunfelder-- an expert in drug induced ocular side effects-- explained, "if you read on though it shows inferior pole bran of the op-- left optic disc which could be early papilledema." Fraunfelder Dep. 195:8-195:11, Ex. G3. The patient also exhibited "progressive peripheral deterioration OU", intracranial imaging revealed "no abnormality but empty sella", and "with dynamic measurement CSF OP increased up to 70 cm H20." Martínez et al., Ex. A27. There can be no serious dispute that this patient met the diagnostic criteria for PTC/IH. Finally, the physicians recommended removal. *Id.* Bayer's superficial attempt to exclude this report is likely founded in the patient's "atypical", *i.e.* non-obese, presentation, which cuts squarely against Bayer's position that Plaintiff's weight, not levonorgestrel was the cause of her PTC/IH.

Next, Bayer contends that Dr. Fraunfelder may not reliably cite to several Bayer clinical trial cases, such as one allegedly involving a woman "who developed IIH after nearly six years of Mirena use and who recovered with Mirena still in place." *Id*. This is highly misleading, as the patient was enrolled in a trial investigating insertion of a second consecutive Mirena. MIR_PIEU_00774311, Ex. B9. Thus, "nearly six years" is properly characterized as "ten months" into her second Mirena. *Id.* Likewise, Bayer misrepresents "another case involv[ing] a woman who developed IIH three years before using a non-Mirena IUD and [whose] IIH remained stable while her IUD was in place." [DN 66] at 24. Tellingly, rather than cite the clinical trial data itself, Bayer cites its own interpretation of this case framed to disprove a safety signal for PTC/IH. MIR_PKEU_00699321, Ex. B10. The "non-Mirena IUD" in question was an LCS12 (Skyla), another LNG-IUD produced and marketed by Bayer, and there is no documentation whether levonorgestrel was used previously. MIR_JSEU_00159741, Ex. B7.

Furthermore, the patient underwent stent placement (which drains the cerebrospinal fluid from the brain) for treatment of PTC/IH, improving despite continued IUD placement. *Id.* Bayer's other criticisms concerning "recovery without removal", "non-Mirena cases", and "no positive rechallenge" rely on similar specious misrepresentations of the underlying reports and Plaintiff's experts' testimony about them.

Furthermore, Dr. Fraunfelder's review of spontaneous reports in the WHO database is reliable. As described in detail *supra*, Dr. Fraunfelder is extremely qualified to analyze WHO data. Dr. Fraunfelder's analysis does not consist of his *ipse dixit* conclusions as Bayer suggests; rather, he "highlight[s] the gestalt of the body of reports." Fraunfelder Dep. at 153:14-153:15, Ex. G3. His adjudication process involves highlighting the summary of the reports, discarding duplicate reports, and discarding reports that are clearly related to another disease. *Id.* at 153:15-153:20. Moreover, Dr. Fraunfelder establishes that a single case report alone "could be a very strong signal that will be the only data we ever have on a drug causing a side effect." *Id.*, at 23:6-23:9. This is because "some things are extremely rare [ ], and sometimes you don't have any data during preclinical studies and it's not until it's marketed to millions of people that you get something that occurs in one out of a million that it becomes a significant side effect." *Id.*, at 28:15-28:24.

Additionally, Bayer argues that Dr. Fraunfelder's opinion is called into doubt based on the use of a single word, "possible", in his book. [DN 66] at 26 (citing Fraunfelder et al., DRUG-INDUCED OCULAR SIDE EFFECTS). Critically, the book was published prior to the introduction of significant scientific evidence of causation in the medical community. Fraundfelder Dep. 234:13-235:3, Ex. G3; *see also* Publishing Details, Ex. A40. Dr. Fraunfelder elaborated that he is not yet prepared to classify the relationship for the 8th edition of his book, as "there's a lot of data

coming to light", but he thinks it "is a more likely than not." Fraunfelder Dep. at 235:4-235:15, Ex. G3. Moreover, Dr. Fraunfelder testified that in forming his opinions here, he "follow[ed] all of the same processes and methods and procedures that [he] normally use[s] in making conclusions" for his book[.]" *Id.* at 245:5-245:10. Dr. Fraunfelder's opinions have reliable bases, and Bayer's motion to exclude his opinions should be denied.

B. Dr. John Maggio

Bayer criticizes Dr. Maggio's proposed mechanism; yet, the "risk factors" for PTC/IH that Bayer itself points to do not even have a known mechanism. As a sister court within this circuit recently agreed with the Eastern District of New York, an expert need not proffer a definitive mechanism, but rather "a plausible mechanism that has been identified based on his professional understanding of the relevant literature." *Kruszka v. Novartis Pharms. Corp.*, 28 F. Supp. 3d 920, 940 (D. Minn. 2014) (citing *Deutsch v. Novartis Pharms. Corp.*, 768 F. Supp. 2d 420, 439-40 (E.D.N.Y. 2011)) ("permitting testimony about a plausible hypothesis about a causation mechanism where the 'hypothesis has been deemed plausible and credible in the relevant medical literature, and is well within [the expert's] field of expertise based on his training, experience, and history of publication')". In fact, scientists have described as "plausible" a role for sex hormones (of which LNG is one is a potent synthetic one), in the pathophysiology of PTC.[33] Further, the mineralocorticoid mechanism outlined by Dr. Maggio has been endorsed by researchers as a plausible manner by which *all* PTC cases may be explained.[34] This is sufficient to demonstrate biological plausibility under *Daubert*.

It is well established that pharmacological activities may be predicted based on the

[33] Chen et al., *Sex Disparities in Neuro-Ophthalmologic Disorders*, 40 Current Eye Research 247, 248 (2015), Ex. A38.
[34] Andrews et al., *Idiopathic Intracranial Hypertension and Obesity*, 81 Horm Res Paediatr 217, 219 (2014), Ex. A35; Salpietro & Ruggieri, *Pseudotumor Cerebri Pathophysiology: The Likely Role of Aldosterone*, 54 Headache 1229 (2014), Ex. A37.

binding affinities of drugs or hormones for various receptors. "Besides the progestogenic effect, which is in common for all progestins, there is a wide range of biological effects, which are different for the various progestins and have to be taken into account, when medical treatment is considered."[35] Bayer's claims that it is not accepted pharmacological practice to anticipate the effects of progestins based upon their binding affinities is entirely contrary to every piece of literature on the subject of binding affinities and progestins.

In addition to these absurd claims, Bayer argues that Dr. Maggio's opinion is unreliable because he "speculates" that LNG is an agonist, allegedly "admitting" that he cannot point to any literature that says LNG is an agonist. This is not true. Dr. Maggio merely admits that the question is not settled: "LNG clearly interacts with the mineralocorticoid receptor, but whether it is an agonist or antagonist or partial agonist at this receptor is unclear from the available literature (Sitruk-Ware, Hum. Reprod. Update 12: 169-178, 2006; Africander et al., Steroids 76: 636-652, 2011; Stanczyk et al., Endocrine Rev. 34: 171-208, 2013)." Maggio Report p. 17-18, Ex. J1. Dr. Maggio then spends a more substantial portion of his report explaining that mineralocorticoid agonism by LNG is *reasonable*, as "[others] have reported that while LNG is clearly not an antagonist, whether or not it is an agonist is unsettled." *Id.*, at 43. Further, LNG does not act like drospirenone, an MR antagonist, in the presence of estrogen; binds with high affinity to MR, suggesting it is an agonist at MR; and "as noted by Kuhl the norgestimate metabolites (levonorgestrel-3-oxime and levonorgestrel-17β-acetate) which are metabolically converted to LNG are both agonists at the MR. Thus the possibility that LNG is an agonist at

[35] Schindler et al., *Classification and pharmacology of progestins*, 46S1 Maturitas S7, S7 (2003) (article generally discussing the possible side effects of several progestins, based on binding affinities and agonism), Ex. A18. *See also, e.g.*, Herber Kuhl, *Comparative Pharmacology of Newer Progestogens*, 51 Drugs 188 (1996) (describing in minute detail the properties of various progestins based upon binding affinities and agonisms), Ex. A12; Regine Sitruk-Ware, *New progestagens for contraceptive use*, 12 Human Reproduction Update 169 (2006) (describing the quest to find new progestins that bind more selectively in order to reduce side effects), Ex. A23.

MR seems reasonable." *Id.*, internal citations omitted.

Yet, at his deposition, defense counsel attempted to trick Dr. Maggio with a study by Moore et al. which reports that LNG does have anti-mineralocorticoid activity, but this article actually misquotes its sources.[36] Maggio Depo 266:4-267:18, Ex. J3. And as pointed out in Dr. Jusko's (Bayer's pharmacology expert) deposition, the allegedly "inconclusive" results reported by Africander et al. are equally spurious, as they have also cited only to studies stating that LNG is *not* an antimineralocorticoid. Jusko Depo 209:22-222:13, Ex. Q1; *see also* Exhibits 17-22 to Jusko Deposition, attached collectively hereto as Exhibits Q2-7. In fact, one of the studies Africander et al. cite to, *Krattenmacher*, was published by a Bayer scientist (who happened to be heavily involved in the Mirena FDA approval application) and found that LNG is not an antimineralocorticoid.[37] Far from making baseless or speculative claims regarding LNG's agonism at the MR, Dr. Maggio appropriately analyzes the available evidence to conclude that this mechanism is biologically plausible. Accordingly, Bayer's motion to exclude this opinion should be denied.

C. Dr. David Ross

[36] Moore et al., *Multiple nuclear receptor signaling pathways mediate the actions of synthetic progestins in target cells*, 357 Molecular and Cellular Endocrinology 60, 64 tbl. 1 (2012) (listing levonorgestrel as an "antimineralocorticoid") (citing Africander et al., *Molecular mechanisms of steroid receptor-mediated actions by synthetic progestins used in HRT and contraception*, 76 Steroids 636, 639 tbl. 2 (2011) (results inconclusive), Ex. A28), Ex. A33; Botella et al., *Lack of estrogenic potential of progesterone- or 19-nor-progesterone-derived progestins as opposed to testosterone or 19-nor-testosterone derivatives on endometrial Ishikawa cells*, 55 J. Steroid Biochem. Mol. Biol. 77 (1995) (mineralocorticoid activity not discussed), Ex. A8; Garcia-Becerra et al., *Comparative evaluation of androgen and progesterone receptor transcription selectivity indices of 19-nortestosterone-derived progestins*, 91 J. Steroid Biochem. Mol. Biol. 21 (2004) (mineralocorticoid activity not discussed), Ex. A19; Kuhl, *Pharmacology of estrogens and progestogens: influence of different routes of administration*, 8(S1) Climacteric 3, 32 tbl. 9 (2005) (**not** an antimineralcorticoid), Ex. A48; Kumar et al., *Nestorone: a progestin with a unique pharmacological profile*, 65 Steroids 629 (2000) (mineralocorticoid activity not discussed), Ex. A16; Mueck & Sitruk-Ware, *Nomegestrol acetate, a novel progestogen for oral contraception*, 76 Steroids 531, 533 tbl. 3 (2011) (**not** an antimineralcorticoid), Ex. A30; Philibert et al., *The pharmacological profile of a novel norpregnance progestin (trimegestone)*, 13 Gynecol. Endocrinol. 316 (1999) (mineralocorticoid agonism/antagonism not discussed for LNG), Ex. A13; Schindler et al., *Classification and pharmacology of progestins*, 46 Maturitas S7 (2003) (**not** an antimineralcorticoid), Ex. A18).

[37] Rolf Krattenmacher, *Drospirenone: pharmacology and pharmacokinetics of a unique progestogen*, 62 Contraception 29, 29 (author affiliated with Schering, Bayer's predecessor company), 31 tbl. 2 (finding that LNG is **not** an antimineralocorticoid) (2000), Ex. A15.

Dr. Ross's disproportionality analysis in his report is reliable. Any alleged differences between Dr. Ross's expert report and his deposition testimony goes not to the reliability of his opinions, but the credibility of his testimony. Perceived "[i]nconsistencies in expert testimony do not warrant exclusion under Rule 702; rather, they are appropriate topics for cross-examination." *Ergotron, Inc. v. Rubbermaid Commer. Prods.*, LLc, No. 10-2010 ADM/JJG, 2012 U.S. Dist. LEXIS 121795, at *38-39 (D. Minn. Aug. 28, 2012). Likewise, Dr. Ross's disproportionality analysis is not excludable on this basis. Furthermore, even if this Court were to exclude his disproportionality analysis, Dr. Ross has opined that it is not critical to his conclusions about the causal connection. *See* Ross Depo 18:15-24, 30:11-16; 409:22-410:15, Ex. M3. Dr. Ross's disproportionality analysis comprises, at best, two pages of his 86-page report, in which he discusses numerous pieces of evidence to support his contention that there is reasonable evidence of a causal relationship between Mirena and PTC/IH.

D. Dr. Rosa Tang

Dr. Tang absolutely concludes that general causation exists in this case, despite Bayer's contentions. In its selective citation to case law, Bayer merely stresses its own interpretation of Dr. Tang's word choice, conveniently ignoring Dr. Tang's own elucidation as to her ultimate conclusion. Deceptively, Bayer seeks to have Dr. Tang's testimony excluded based on just one of three days of Dr. Tang's testimony in this and other cases. Despite Plaintiffs' counsel's understanding that Dr. Tang would be deposed on general causation followed by separate depositions for each individual plaintiff in the Mirena PTC litigation, Bayer's counsel insisted upon combining general causation with the first of several plaintiffs, disorienting Dr. Tang's opinions. *See* 05/03/16 Email, Ex. N5; Tang 05/10/16 Dep. 98:1-98:24, Ex. N3. When Plaintiffs' counsel expressed concern with this tactic, Bayer's counsel, Ms. Cook, asserted that she had seven hours "to spend however I want on generic issues and the Houston case", and that

she was going to "break it down however it breaks down, because there's no agreement about that. We have seven hours, and I'll just spend it however it makes sense. If it gets confusing, the witness will let me know." *Id.*, at 98:5-98:24. Yet, when Dr. Tang was deposed one week later regarding four separate plaintiffs, (not yet including Ms. Miller), Bayer's counsel insisted off the record upon separate transcripts for each case. Prior to Dr. Tang's testimony on the second day, Plaintiffs' counsel noted the impropriety of this strategy on the record, insisting that it would not accurately preserve Dr. Tang's general causation testimony in each case. Tang 05/17/16 Dep. 12:11-13:5. Ex. N4. At this insistence, Bayer's counsel agreed to a combined record. *Id.*, at 13:11-13:17. Critically, elsewhere during Dr. Tang's examination, Dr. Tang explained: "I have been trying to point out that I mean association and not the only cause, because there are other factors that are playing a role." *Id*., at 170:4-170:7. Clearly this is not an admission that Dr. Tang "cannot claim Mirena *causes* IIH," but rather a clarification that in certain cases causation is multifactorial. Tang Rpt. at 10, Ex. N1; *see also* Tang 05/17/16 Dep. 174:7-174:23, Ex. N4.

Furthermore, Bayer's own citations reveal misplaced reliance on a term of art, rather than on the substance of Dr. Tang's actual opinion. For example, Bayer cites *Nelson v. Am. Home Prod. Corp.*, for the idea that evidence of association "is not proof of causation in the courtroom or the scientific community." 92 F. Supp. 2d 954, 969 (W.D. Mo. 2000). Yet, that discussion focused quite clearly on causation opinions founded entirely in spontaneous adverse event reports. The Court explained, in the context of the case-specific facts that, "[w]hile such case reports may be relevant to the question of whether Defendants had notice of the possible ocular side effects [ ], they are not, *without more*, reliable evidence of causation." *Id.* (emphasis added). As explained above, there is certainly more than case reports here, and in any event Dr. Tang's use of the word association in this context has nothing to do with case reports.

Likewise, Bayer suggests that the Eighth Circuit, in the toxic tort case *Sorensen by & Through Dunbar v. Shaklee Corp.*, held accordingly; yet, Bayer fails in its astoundingly imprecise citation to clarify that the quotation to which it points the Court is a footnote citing to a law review note. *See i.e.*, 31 F.3d 638, 643 n.8 (8th Cir. 1994) (citing Steve Gold, *Causation in Toxic Torts: Burdens of Proof, Standards of Persuasion, and Statistical Evidence,* 96 Yale L.J. 376, 380 (1986) (footnote omitted)). First, in the footnote at issue, the Court explains, "*epidemiological studies may only report* an association between an injury or disease and a specific exposure *which* is not necessarily one of cause and effect." *Id*. (emphasis added). Thus, because of this valid concern, the Court continues (quoting Mr. Gold), "'[i]n an individual case, epidemiology cannot conclusively prove causation [. . .]" *Id*. Yet, as Mr. Gold notes in the original: "With proper scientific interpretation, these correlations lend great weight to an inference of causation." NOTE: Causation in Toxic Torts: Burdens of Proof, Standards of Persuasion, and Statistical Evidence., 96 Yale L.J. 376, 380. Again, as with *Nelson*, Bayer's citation to *Sorenson* – even if correctly applied – is not dispositive because, as explained above, Dr. Tang never once referred to a statistical association. Clearly Dr. Tang's multifactorial model indicating Mirena as a substantial cause, "and not the only cause," is not incompatible with that court's finding. Bayer's motion to exclude Dr. Tang's opinions should be denied.

CONCLUSION

For the foregoing reasons, the Bayer Defendants' Omnibus Motion to Exclude General Causation and Labeling Experts of Plaintiffs' Experts should be denied.

Respectfully submitted,
JONES WARD PLC

/s/ Lawrence L. Jones II
Lawrence L. Jones II (*Pro Hac Vice*)
312 S. Fourth St., 6th Floor

Louisville, Kentucky 40202
Tel: (502) 882-6000 | Fax: (502) 587-2007
larry@jonesward.com

D. Todd Mathews
Gori Julian & Associates PC
156 N. Main Street
Edwardsville, IL 62025
(618) 659-9833
todd@gorijulianlaw.com

Counsel for Plaintiff

CERTIFICATE OF SERVICE

I hereby certify that that the undersigned has served all counsel of record via the Court's ECF/CM system on November 5, 2016.

/s/ Lawrence L. Jones II
Lawrence L. Jones II