No. 14-958

IN THE

Supreme Court of the United States

MARIANNE CHAPMAN, ET VIR.,

Petitioners,

v.

PROCTER & GAMBLE DISTRIBUTING LLC., ET AL.,

Respondents.

On Petition For A Writ Of Certiorari To The United States Court of Appeals For The Eleventh Circuit

RESPONDENTS' BRIEF IN OPPOSITION

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CORPORATE DISCLOSURE STATEMENT

Pursuant to Supreme Court Rule 29.6, Respondents make the following disclosures:

Respondent The Procter & Gamble Distributing LLC is an indirect, wholly owned subsidiary of The Procter & Gamble Company.

Respondent The Procter & Gamble Manufacturing Company is a direct, wholly owned subsidiary of The Procter & Gamble Company.

The Procter & Gamble Company is publicly traded. No entity owns more than 10% of the stock of The Procter & Gamble Company.

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RESPONDENTS' BRIEF IN OPPOSITION

Marianne and Daniel Chapman construct their entire petition for certiorari around an alleged circuit split on the question whether Federal Rule of Evidence 702 "permits a district court to *require* epidemiological evidence as a *precondition* for admissibility" of expert opinion testimony on general causation in toxic-tort cases. Pet. i (emphasis added). This circuit split, however, does not exist, and this case would not implicate it in any event.

I. The Chapmans' alleged circuit split is illusory. Contrary to their assertions—and in direct answer to their Question Presented—the Eleventh Circuit "has long held that epidemiology is not required to prove causation in a toxic tort case." *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1199 (11th Cir. 2002); *see also id.* at 1198 ("It is well-settled that while epidemiological studies may be powerful evidence of causation, the lack thereof is not fatal to a plaintiff's case."); *Kilpatrick v. Breg, Inc.*, 613 F.3d 1329, 1336-37 (11th Cir. 2010) ("The absence of such evidence [epidemiological studies] is not fatal, but makes [an expert's] task to show general causation more difficult." (citing *Rider*, 295 F.3d at 1198-99)).

The Chapmans neither cite nor acknowledge this binding Eleventh Circuit precedent, but instead focus on a single statement in the panel opinion below that they claim "require[s] epidemiological evidence as a precondition" for admission of expert testimony on general causation. Pet. i. However, the *Chapman* panel simply did not have the power to overrule a settled line of Eleventh Circuit precedent. Nor did it purport to do so: The panel decision (a) repeatedly embraces circuit precedent, Pet. App. 11a,

16a, 27a, 34a (citing *Rider* and *Kilpatrick*); (b) recognizes that an admissibility determination under Rule 702 "is 'a flexible one,'" *id.* at 13a (quoting *Daubert v. Merrill Dow Pharms., Inc.*, 509 U.S. 579, 594-95 (1993)); (c) addresses five different kinds of potentially reliable scientific methodologies, including but not limited to epidemiological studies, that might have supported admissibility here, *id.* at 15a ("The [district] judge determined the Chapmans' experts did not satisfy any of these recognized methodologies."); and (d) affirms, under an abuse of discretion standard, a district court decision that painstakingly examined all of the evidence underlying the general-causation opinions of the Chapmans' proposed experts, *id.* at 15a-19a. Considered in context and in its entirety, the panel decision cannot fairly be read as imposing a categorical rule that general-causation experts must rely on epidemiological studies.

Nor does the law of other circuits suggest the circuit split alleged by the Chapmans. In fact, the lead case that they identify on their side of the purported split—*Milward v. Acuity Specialty Products Group, Inc.*—actually cited the Eleventh Circuit's decision in *Rider* as the case-law support for its conclusion that "[e]pidemiological studies are not per se required as a condition of admissibility." 639 F.3d 11, 24 (1st Cir. 2011). And the Fifth Circuit, which the Chapmans claim mandates that experts must rely on epidemiological evidence, has recognized the importance of such evidence but nonetheless expressly disavowed any categorical rule. *See, e.g.*, *Brock v. Merrell Dow Pharma.*, 874 F.2d 307, 313 (5th Cir. 1989) ("While we do not hold that epidemiological proof is a necessary element in all

toxic tort cases, it is certainly a very important element.").

II. Putting aside the lack of any circuit split, this case is a poor vehicle in which to consider the Question Presented because the Court's resolution of that question would not affect the outcome here.

First, the district court held that the Chapmans had failed to present admissible evidence of either general causation, Resp. App. 8a-41a,[1] *or* specific causation, *id.* at 41a-46a, and the Eleventh Circuit affirmed both holdings, Pet. App. 14a-19a (general causation); *id.* at 19a-25a (specific causation). Because the lack of *specific*-causation expert testimony is an independent ground adequate to support the grant of summary judgment, this Court's resolution of the Question Presented concerning *general* causation will not impact the outcome of this case.

Second, even as to general causation, the Chapmans have not identified any legal error in the district court opinion, which acknowledged (consistent with Eleventh Circuit precedent) that epidemiological evidence was not a precondition of admissibility. Resp. App. 9a-10a, 16a-17a. Because the district court did *not* apply the categorical rule attacked by the Chapmans, the outcome of this case will not be affected even if the Court resolves the Question Presented in their favor.

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[1] The petition omits the district court's *Daubert* opinion, which is central to their admissibility-based Question Presented. That opinion is attached as an Appendix to this Brief in Opposition and is cited as "Resp. App." herein.

RESTATEMENT OF THE CASE

A. Marianne Chapman's Disease

Zinc is an essential nutrient. It fortifies milk, yogurt, chicken, grains and other healthy foods. And it is critical to human growth and development. *See* Pet. App. 3a. In fact, inadequate zinc intake can lead to a host of medical problems including growth retardation, brain dysfunction, anorexia, and impaired immune function.

In 1990, respondent Procter & Gamble [2] reformulated its popular denture cream Fixodent to include a calcium-zinc compound to improve its hold, which is the main reason people use denture adhesive. *Id.* at 2a. This calcium-zinc compound "is less bioavailable than other zinc compounds." *Id.*[3]

Nearly two decades later, in 2008, a case report hypothesized that zinc in denture cream *may* lead to copper deficiency, which in turn *may* lead to neuropathy. *Id.*[4] Thereafter, various individuals

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[2] As used herein, "Procter & Gamble" refers collectively to respondents The Procter & Gamble Distributing LLC and The Procter & Gamble Manufacturing Company.

[3] Free-standing zinc is not found in nature; rather, zinc occurs in various compounds. Pet. App. 2a. These compounds are not interchangeable: Their different chemical structures affect zinc's bioavailability—i.e., how zinc is absorbed and stored in a body or made available for use by the body. *See* Resp. App. 31a n.39.

[4] S.P. Nations, *et al.*, *Denture Cream: An Unusual Source of Excess Zinc, Leading to Hypocupremia and Neurologic Disease*, 71 NEUROLOGY 639 (2008) ("Nations Case Report"). The authors acknowledged that their case report findings did "not prov[e] a causal relationship" between denture cream and neurological disease, and further that "the mechanism by which hypocupremia [copper deficiency]

filed lawsuits against Procter & Gamble and other denture cream manufacturers. *Id.* at 3a. One such suit was filed by the Chapmans, who claim that Ms. Chapman's use of Fixodent caused her to develop a copper deficiency, which in turn caused her to develop a neurological condition known as a myelopathy, which is a spinal-cord disorder. *Id.* at 1a-2a.[5]

Ms. Chapman's claim conflicts with her medical history, which is rife with neurologic complaints dating back to her childhood, long before she began using Fixodent in 2001. *Id.* at 20a, n.12. For example, Ms. Chapman suffered from frequent migraine headaches and sought treatment for unexplained foot and ankle pain as a child. *Id.* She was evaluated again as a teenager for pain that extended from her shoulder through her leg. *Id.* And after a series of recurrent falls (some of which resulted in hospitalization), she complained of pain in her lower extremities, numbness and decreased sensation. *Id.* Similar neurologic complications continued through Ms. Chapman's adulthood when, prior to her denture cream use, she was diagnosed with hereditary hemorrhagic telangiectasia, a

(continued…)

leads to neurologic abnormality in humans remains uncertain." *Id.* at 641-42.

[5] This is not the same condition as the patients covered by the Nations Case Report. As an author of that report explained, "'the patients in our study had more of a neuropathy than a myelopathy.'" Resp. App. 32a (quoting testimony of Dr. Philip Boyer).

genetic disorder often accompanied by neurologic complications involving the spinal cord. *Id.*

After Ms. Chapman began using Fixodent, she again complained of pain in her lower extremities. *Id.* at 21a, n.14. She was diagnosed with and treated for Vitamin B12 deficiency, which has been associated with myelopathy. *Id.* After temporary improvement, Ms. Chapman's neurologic complications returned in 2006, when she experienced burning and numbness in her legs, poor balance, and eventually developed loss of motor control in her right hand. *Id.* Also in 2006, Ms. Chapman developed anemia (low red blood cells) and neutropenia (low white blood cells). *Id.*

Ms. Chapman stopped using Fixodent in January 2009. Nevertheless, she continued to have anemia until at least May 2009. *Id.* at 21a, n.15. Moreover, she had normal red and white blood cell measurements in May and again in November 2006, while she was still using Fixodent, and her neutropenia normalized permanently in September 2008, several months *before* she stopped using Fixodent. *Id.* at 21a, n.14. Furthermore, Ms. Chapman's neurological symptoms continued well after she stopped using Fixodent—indeed, some worsened. For example, ten months after she stopped using Fixodent, Ms. Chapman reported worsening hand weakness and wrist drop. *Id.* at 21a, n.15. And in 2011 (two years after she stopped using Fixodent), she had a recurrence of a neurological complication—a Romberg sign (unsteady balance with closed eyes)—that was not present in 2010 (one year after she stopped using Fixodent). *Id.*

As the foregoing demonstrates, no strict temporal relationship exists between Ms. Chapman's symptoms and her Fixodent use. Moreover, Ms. Chapman was never diagnosed with copper deficiency myelopathy ("CDM") by her treating physicians prior to the filing of her lawsuit, nor did those treating physicians diagnose denture cream as the cause of her neurologic symptoms. *Id.* at 20a. In fact, she was not diagnosed with CDM until she was examined by the specific-causation expert whom the Chapmans retained for this litigation (Dr. Greenberg). *Id.*

B. The District Court's Decision

The Chapmans tendered a string of experts (Drs. Brewer, Landolph, Lautenbach, and Greenberg) in an effort to construct a novel, multi-step causal chain linking Fixodent to myelopathy. Procter & Gamble moved to exclude these witnesses because they did not employ reliable methodologies in reaching their opinions about general or specific causation, rendering those opinions inadmissible under Rule 702 and *Daubert*.

Before ruling on Procter & Gamble's *Daubert* motions, the district court meticulously reviewed all the evidence presented by the parties, including 18 different expert reports, 23 substantive briefs, and numerous deposition transcripts, exhibits and scientific literature, comprising thousands of pages in total. The district court then conducted a full-day *Daubert* hearing. After all of this, the court issued a thorough 39-page opinion (its "*Daubert* opinion") holding that the Chapmans' expert witnesses on both general causation (*i.e.*, whether Fixodent *can* cause myelopathy) and specific causation (*i.e.*, whether

Fixodent *did* cause Ms. Chapman's myelopathy) lacked scientifically reliable bases for their opinion testimony.

The district court first explained that "[a] survey of Eleventh Circuit *Daubert* jurisprudence in toxic-tort cases identifies several types of evidence and methodologies that have been described as reliable bases for an inference of general causation." Resp. App. 9a. "Those types of evidence and methodologies are drawn from toxicology and epidemiology and include the dose-response relationship, epidemiological studies, the amount of background risk of the disease, an understanding of the physiological mechanisms involved, and clinical studies or tests." *Id.* at 9a-10a. The court made clear, however, that "[a] plaintiff need not provide evidence of each above-described type." *Id.* at 10a. In fact, the court evaluated *all* of the evidence and methodologies employed by the Chapmans' experts, regardless of type or classification, in its detailed *Daubert* opinion.

First, the district court addressed dose-response. The court explained that "[b]ecause all substances have the potential to be toxic, '"the relationship between dose and effect (dose-response relationship) is the hallmark of basic toxicology,"' and '"is the single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect."'" *Id.* at 11a (quoting *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1242 (11th Cir. 2005), itself quoting David Eaton, *Scientific Judgment and Toxic Torts: A Primer in Toxicology for Judges and Lawyers*, 12 J.L. & POL'Y 1, 11, 15 (2003)). The court observed that "[o]ften '"low dose

exposures—even for many years—will have no consequence at all, since the body is often able to completely detoxify low doses before they do any damage."'" Resp. App. 11a (quoting *McClain*, 401 F.3d at 1242, itself quoting Michael D. Green, *et al.*, *Reference Guide on Epidemiology*, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 390 (Fed. Judicial Center, 2d ed. 2000)). Moreover, the court noted, "[t]his . . . is almost certainly true of Fixodent, which, as even Plaintiffs seem to concede, is safe when used in moderate amounts." *Id*.

The court then explained that "neither Plaintiffs' experts nor the articles on which they rely determine how much Fixodent must be used for how long to increase the risk of a copper-deficiency, or for how long a copper-deficiency must persist before an individual is at an increased risk of developing a myelopathy." *Id.* at 12a. Thus, the court concluded, "there is no dose-response evidence which Plaintiffs' experts may use to reliably infer what type of exposure level to Fixodent is necessary to induce a negative copper balance, to cause a copper deficiency, or to cause a myelopathy." *Id.* at 15a.

Second, the district court turned to epidemiological evidence. The court explained that "[e]pidemiology is the 'best evidence of causation in toxic tort cases.'" *Id.* at 16a (quoting *Kilpatrick*, 613 F.3d at 1337 n.8). Noting that the Chapmans' experts "have no analytical epidemiological evidence on which to base their inference of causation," the court observed that they instead sought to prove general causation through "descriptive epidemiological evidence, like case studies, and a plausible biological explanation." *Id.* at 16a-17a. While specifically stating that "in the

appropriate case, case studies may provide reliable evidence of causation," the court concluded that "this is not an appropriate instance" because "the case studies Plaintiffs' experts rely on suffer from a number of inaccuracies and methodological weaknesses that undermine their evidentiary value." *Id.* at 17a. *See also id.* at 28a-38a (detailing the inaccuracies and weaknesses). Moreover, the court recognized, "the lack of *any* analytic epidemiological studies does weaken Plaintiffs' experts' assertion of causation." *Id.* at 23a, n.28 (emphasis in original).

Third, the district court turned to evidence regarding the background risk of disease. The court observed that "[a]n important aspect of epidemiological reasoning is knowledge of background risk," which is "'the risk a plaintiff and other members of the general public have of suffering the disease or injury that plaintiff alleges *without* exposure to the drug or chemical in question.'" *Id.* at 18a (quoting *McClain*, 401 F.3d at 1243) (emphasis in original). "[O]ne must know the background prevalence of a disease before one can determine if exposure to an agent has increased the risk of that disease." *Id.* Otherwise, "[w]ithout a baseline, any incidence may be coincidence." *Id.* at 21a. The Chapmans' causation experts, however, "uniformly testified that they did not know the background risk of copper-deficiency myelopathy." *Id.* at 18a. This, the Court explained, was "a serious methodological deficiency" and "the absence of this data [wa]s a substantial weakness in Plaintiffs' experts' causal reasoning." *Id.* at 18a-19a, 21a.

Fourth, the district court considered the physiological processes by which the Chapmans'

experts opined that Fixodent caused CDM. The court acknowledged that the experts provided some physiological explanations for how excessive bioavailable zinc could cause a copper deficiency, but "this support[ed] only one premise in Plaintiffs' multi-step hypothesis," without either explaining how copper deficiency can lead to neurological abnormalities or accounting for "the limited bio-availability of the zinc in Fixodent." *Id.* at 22a.

Fifth, the district court addressed clinical studies. The court noted that the experts had very little clinical evidence, though it also held that "the lack of a randomized, controlled experimental study showing that Fixodent causes copper-deficiency myelopathy does not undermine Plaintiffs' experts' inference of causation." *Id.* at 23a.

After discussing the accepted methodologies for proving general causation in toxic-tort cases, the district court focused on the evidence upon which the Chapmans' experts relied, including case reports, de-challenge data, biological plausibility, an FDA Notice and Recommended Action, as well as animal studies "mentioned in passing" in expert reports. *Id.* at 39a. The court carefully analyzed all of this evidence. *Id.* at 24a-41a.

As the court explained, "Plaintiffs' experts' conclusion that Fixodent can cause copper-deficiency myelopathy is almost entirely based on the information contained in a number of scientific articles reporting cases of patients who used denture creams who also had abnormal levels of zinc and copper in their blood and neurological symptoms." *Id.* at 28a-29a. The court observed that while "'[c]ausal attribution based on case studies must be regarded

with caution,'" *id.* at 29a (quoting Green, REFERENCE MANUAL 475), "the Eleventh Circuit has not foreclosed using case reports as supporting an inference of causation when accompanied by other proof of causation," *id.* at 29a-30a. However, the court continued, "there [were] a number of particular problems with the case reports relied on by Plaintiffs' experts in this case." *Id.* at 30a. Those included the facts that most of the case studies involved patients who used a denture adhesive other than Fixodent and/or who did not have CDM; that the case studies themselves contained inaccuracies; and that in the only case in which a person reported having used Fixodent exclusively, the person had near-normal zinc levels and had been diagnosed with a condition other than CDM. *Id.* at 30a-38a.

Based on these various flaws, the district court held that the case reports cited by the Chapmans' experts were an unreliable basis for opining on causation. *Id.* at 38a. And after similarly finding the experts' other evidence unreliable or insufficient to support an opinion on general causation, the district court exercised its broad discretion as a gatekeeper and excluded all of the Chapmans' general causation experts. *Id.* at 38a-41a.

Finally, the district court held that the Chapmans' expert on specific causation (Dr. Greenberg) did not perform a reliable differential diagnosis of Ms. Chapman. *Id.* at 46a. Dr. Greenberg opined that Fixodent caused Ms. Chapman's myelopathy, but there was no independent, scientifically reliable evidence that the calcium-zinc compound in Fixodent can cause myelopathy that would have allowed Dr. Greenberg to "rule-in" Fixodent as a potential cause

of Ms. Chapman's disease. *Id.* at 43a. In addition, Dr. Greenberg failed adequately to explore potential causes of Ms. Chapman's myelopathy other than Fixodent. *Id.* at 43a-46a. For both reasons, the district court again exercised its broad gatekeeper discretion and excluded Dr. Greenberg's opinion on specific causation.

C. The Initial Appeal To The Eleventh Circuit And Proceedings After Remand

Following the *Daubert* opinion excluding the Chapmans' experts, the parties entered into a stipulated final judgment dismissing the lawsuit but reserving the Chapmans' right to appeal to the Eleventh Circuit. However, the Eleventh Circuit held that the Chapmans lacked standing because they were not adverse to the final judgment. Pet. App. 6a-7a; *see also Chapman v. Proctor & Gamble Distrib., LLC*, No. 11-13371, at 2 (11th Cir. Jan. 4, 2012) (per curiam). Thus, the Eleventh Circuit dismissed the appeal. Pet. App. 7a.

On remand, the district court granted the Chapmans' motion to vacate the stipulated final judgment under Federal Rule of Civil Procedure 60(b). *Id.* Procter & Gamble thereafter moved for summary judgment, which the district court granted over opposition. *Id.*

D. The Second Appeal To The Eleventh Circuit

The Chapmans again appealed to the Eleventh Circuit. Reviewing the district court decision for an abuse of discretion, *see General Electric Co. v. Joiner*, 522 U.S. 136, 141-43 (1997), a panel of the Eleventh Circuit affirmed in all respects.

The *Chapman* panel first considered the Chapmans' argument that the district court should not have conducted a full *Daubert* inquiry because there is a general consensus in the medical community that ingestion of zinc causes CDM. Pet. App. 8a. [6] The *Chapman* panel held that the Chapmans "fail[ed] to show that the zinc compound in Fixodent is . . . [a] medically accepted, cause-and-effect toxin," especially given that "'[m]illions of consumers have regularly used Fixodent for decades without complaint,'" and that "'zinc is undeniably an essential nutrient the body must have to function properly.'" *Id.* at 10a (citation omitted).

Turning to the *Daubert* inquiry itself, the panel recognized both that its review was "only for abuse of discretion," Pet. App. 11a, and that "the [*Daubert*] inquiry is 'a flexible one,'" that involves "'case-specific evidentiary circumstances.'" *Id.* at 13a (quoting *Daubert*, 509 U.S. at 594-95, and *United States v. Brown*, 415 F.3d 1257, 1266 (11th Cir. 2005)). The panel then separately affirmed the

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[6] The Chapmans continue to claim that there is a "broad consensus in the scientific community that zinc in denture cream can cause CDM," Pet. 30, but they continue to cite to sources that merely rely on case reports for their opinions, including the Nations Case Report that the district court's analysis demonstrated was unreliable to support such an opinion, Resp. App. 35a, and another case report hypothesizing that "elevated zinc" may induce copper deficiency *or* may just be "secondary to the copper deficiency state rather than causing copper deficiency." N. Kumar, et al. *Copper Deficiency Myelopathy*, 61 ARCH. NEUROL. 762, 765 (2004). Sources grounded upon case reports are no more reliable than the case reports themselves. *See Glastetter v. Novartis Pharma. Corp.*, 252 F.3d 986, 990 (8th Cir. 2001).

district court's exclusion of the Chapmans' proposed evidence on both general and specific causation.

As to general causation, the panel recognized that the district court "reviewed reliable methodologies, including dose-response relationship, epidemiological evidence, background risk of the disease, physiological processes involved, and clinical studies," and "determined the Chapmans' experts did not satisfy any of these recognized methodologies." Pet. App. 15a. The panel reviewed in detail, and found no basis for setting aside, the district court's conclusion that the Chapmans' experts had presented no evidence of (1) a dose-response relationship between Fixodent and copper deficiency or between copper deficiency and myelopathy; (2) the background risk of CDM in the population generally (by which to gauge whether Fixodent users faced any greater risk of CDM); or (3) any epidemiological studies regarding a connection between zinc and CDM. *Id.* at 16a-18a. In its review, the panel noted prior Eleventh Circuit precedent holding that, in this context, evidence of a dose-response relationship "'is the single most important factor to consider,'" *id.* at 15a-16a (quoting *McClain*, 401 F.3d at 1239); that epidemiological evidence is "'the best evidence of causation,'" *id.* at 15a (quoting *Kilpatrick*, 613 F.3d at 1337 n.8); and that background risk is another "important" consideration, *id.* at 18a (citing *McClain* and quoting the district court). The panel concluded that the district court "did not abuse her discretion or commit manifest injustice by precluding the testimonies of Dr. Brewer, Dr. Lautenbach, and Dr. Landolph as experts on general causation." *Id.* at 19a; *see also id.* at 36a (Jordan, J., concurring) ("Given the due deference that the abuse of

discretion standard embodies, and the range of choice permitted by that standard, I agree that we should affirm the district court's exclusion of the Chapmans' general causation experts" (internal citations and quotation marks omitted)).

The panel then affirmed the district court's exclusion of testimony by Dr. Greenberg, the Chapmans' only expert on the separate issue of specific causation. Dr. Greenberg sought to use a differential diagnosis to opine that zinc in Fixodent caused Ms. Chapman's CDM. *Id.* at 19a. The panel held, however, that "[w]hile differential diagnosis as a scientifically accepted methodology meets the *Daubert* guiding factors for district judges in deciding reliability, Dr. Greenberg did not follow it." *Id.* at 20a (internal citation omitted). As the panel explained, "[g]iven her extensive medical history of neurological problems since childhood, it is entirely possible that Marianne Chapman had the myelopathy condition that she attributes to Fixodent prior to her use of the denture cream, because her symptoms occurred before and after using Fixodent." *Id.* at 22a-23a. Nevertheless, "Dr. Greenberg failed to consider obvious alternative causes for Marianne Chapman's CDM, such as hereditary and acquired conditions known to cause myelopathies," "provided no support for his hypothesis that Marianne Chapman's anemia, neutropenia, and myelopathy resulted from a single cause rather than several causes," and "omitted consideration of idiopathic causes." *Id.* at 24a. Accordingly, the panel held that the district court "did not abuse her discretion or commit manifest error in precluding Dr. Greenberg's expert testimony regarding the specific causation of Marianne Chapman's CDM." *Id.* at 25a.

Finally, the panel concluded that "[b]ecause none of the Chapmans' alternative sources for expert witnesses could provide evidence admissible at trial," the district court correctly granted summary judgment to Procter & Gamble. *Id.* at 35a.

E. Other Courts Addressing The Reliability Of General Causation Opinions Involving Fixodent Have Reached The Same Result

Since the district court excluded the opinion testimony of the Chapmans' experts, several other courts have had occasion to address whether an expert opinion that Fixodent can cause myelopathy is reliable and admissible. All of those cases also involved two or more of the experts employed by the Chapmans here. And the courts in those cases have all reached the same conclusion—that expert opinion testimony of this supposed causal connection is simply too unreliable to be admissible as evidence. *See In re Denture Adhesive Cream Litig.*, No. 4534, 2014 Phila. Ct. Com. Pl. LEXIS 135 (Pa. Ct. Comm. Pl. Feb. 10, 2014); *Jacoby v. Rite Aid Corp.*, No. 1508 EDA 2012, 2013 Pa. Super. LEXIS 5563 (Pa. Super. Ct. Dec. 9, 2013); *Adams v. P&G, LLC*, No. A1204223, 2014 Ohio Misc. LEXIS 3 (Ohio Ct. Comm. Pl. Jan. 22, 2014).

REASONS FOR DENYING THE PETITION

I. THE CIRCUIT SPLIT ALLEGED BY THE CHAPMANS DOES NOT EXIST.

The Chapmans contend that the law of the Eleventh and Fifth Circuits conflicts with the law of the First, Third, Fourth, Ninth, and D.C. Circuits on the question whether epidemiological evidence is "require[d] . . . as a precondition" for admitting expert testimony of general causation in toxic-tort cases. Pet. i, 19. This alleged circuit split, however, simply does not exist.

A. The Eleventh Circuit Does Not Require Epidemiological Studies To Support Expert Opinions On General Causation.

The petition is predicated entirely on attacking a straw man—namely, that the Eleventh Circuit prohibits experts from opining that a substance can cause a disease or injury unless they have epidemiological studies to back up their opinions.[7] This is not the law of the Eleventh Circuit.

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[7] *See, e.g.*, Pet. 1-2 ("[C]ertiorari is warranted because the decision below deepens an existing circuit conflict on the question whether epidemiological evidence is required for an admissible expert opinion on general causation."); *id.* at 2 ("The Eleventh Circuit's rigid requirement of epidemiological evidence is contrary to that limited gatekeeping function."); *id.* at 16 ("[T]he court deemed such [analytical epidemiological] evidence essential to a reliable opinion on general causation."); *id.* at 19 ("Contrary to the decision below, the rule in those five circuits is that the absence of epidemiological evidence is not a valid ground to exclude [an expert opinion]."); *id.* at 28 ("The Eleventh Circuit's holding that epidemiological evidence is 'indispensible' to support a general causation opinion in toxic tort cases is contrary to this Court's precedents

1. The Eleventh Circuit "has long held that epidemiology is not required to prove causation in a toxic tort case." *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1199 (11th Cir. 2002). In *Rider*, the district court excluded expert testimony that the drug Parlodel could cause hemorrhagic stroke as insufficiently reliable to satisfy Rule 702 and *Daubert*. On appeal, the plaintiffs argued that the district court had "erred by requiring epidemiological studies, effectively ruling against them because they could not produce sufficient epidemiological evidence linking Parlodel to stroke." *Id.* at 1198. In response, the Eleventh Circuit explained that "[i]t is well-settled that while epidemiological studies may be powerful evidence of causation, the lack thereof is not fatal to a plaintiff's case." *Id.*

Citing decisions from the Eighth and Tenth Circuits also involving Parlodel, the Eleventh Circuit explained that "[t]hose appellants argued, as the appellants do here, that epidemiological evidence is not required to prove causation. Both courts properly ruled that it was not required." *Id.* at 1199 (citing *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986 (8th Cir. 2001), and *Hollander v. Sandoz Pharmaceutical Corp.*, 289 F.3d 1193 (10th Cir. 2002)). Then, after reiterating that "this Court has long held that epidemiology is not required to prove causation in a toxic tort case," *id.*, the Court concluded that all of the plaintiffs' other evidence

(continued…)

interpreting Rule 702."); *id.* at 29 (describing the Eleventh Circuit's holding as "[r]equiring that all general causation be supported [by] epidemiological evidence").

was insufficiently reliable to support an opinion on causation. *See id.* at 1202 ("In the absence of epidemiology, plaintiffs may still prove medical causation by other evidence. In the instant case, however, plaintiffs simply have not provided reliable evidence to support their conclusions.").

To support the proposition that the Eleventh Circuit had "long held" that epidemiological evidence is not required to prove causation, *id.* at 1199, the *Rider* court cited *Wells v. Ortho Pharm. Corp.*, 788 F.2d 741 (11th Cir. 1986). In that case, the district court admitted expert testimony that spermicide use caused certain birth defects, even though it "found the studies to be inconclusive on the ultimate issue of whether the Product caused Katie Wells' birth defects." *Id.* at 745 (internal quotation marks omitted). In affirming that decision, the Eleventh Circuit, quoting from a D.C. Circuit decision, recognized that:

> a cause-effect relationship need not be clearly established by animal or epidemiological studies before a doctor can testify that, in his opinion, such a relationship exists. As long as the basic methodology employed to reach such a conclusion is sound, . . . products liability law does not preclude recovery until a "statistically significant" number of people have been injured or until science has had the time and resources to complete sophisticated laboratory studies of the chemical.

Id. (quoting *Ferebee v. Chevron Chemical Co.*, 736 F.2d 1529, 1535-36 (D.C. Cir. 1984)). Thus, the Eleventh Circuit held that "[t]he district court properly noted that . . . 'Plaintiffs' burden of proving

that Katie Wells' defects were caused by the Product did not necessarily require them to produce scientific studies showing a statistically significant association between spermicides and congenital malformations in a large population.'" *Id*. (quoting the district court).

Since *Rider*, the Eleventh Circuit repeatedly has reaffirmed that epidemiological evidence, while a significant consideration, is not a precondition for admissibility. *See, e.g.*, *Kilpatrick*, 613 F.3d at 1336-37 ("The absence of such evidence [epidemiological studies] is not fatal, but makes [an expert's] task to show general causation more difficult."); *Hendrix v. Evenflo Co.*, 609 F.3d 1183, 1197 & 1198 n.11 (11th Cir. 2010) (following *Rider*).

2. The Chapmans do not cite any of these holdings in their petition, and, in fact, ignore *Rider*, *Wells* and *Hendrix* entirely. Instead, they focus on a single statement in the *Chapman* panel decision that, they claim, obligates an expert to present epidemiological evidence to avoid exclusion. For several reasons, however, the *Chapman* panel opinion did not—and could not—depart from well-established Eleventh Circuit precedent to create such an obligation.

a. First, as a panel of the Eleventh Circuit, the *Chapman* panel simply did not have the power to overrule any of *Rider*, *Wells*, *Kilpatrick*, or *Hendrix*, much less to overrule all of them in one fell swoop. *See United States v. Steele*, 147 F.3d 1316, 1317-18 (11th Cir. 1998) (en banc) ("Under our prior precedent rule, a panel cannot overrule a prior one's holding . . . ."). Nor did the panel express any intention or desire to do so. Rather, consistent with precedent, the panel acknowledged that a court's

inquiry into the admissibility of expert opinion testimony is "'a flexible one'" that is applied "'in case-specific evidentiary circumstances.'" Pet. App. 13a (quoting *Daubert*, 509 U.S. at 594; *Brown*, 415 F.3d at 1266); *see also id.* at 18a-19a (describing epidemiological studies, background risk evidence and dose-response relationship evidence as "primary methods" for demonstrating general causation, not exclusive or mandatory methods). And the panel specifically cited *Rider*, *Kilpatrick* and *Hendrix* as support for affirming the district court's decision, not as prior opinions to be overruled or ignored. *Id.* at 8a-10a, 13a-16a, 19a, 23a-24a, 31a, 35a, 44a-45a, 48a.

The panel's analysis, moreover, largely tracked the analysis of the district court, which—consistent with Eleventh Circuit precedent—expressly held that the Chapmans' experts were not required to present any specific type of evidence to prove general causation. *See* Resp. App. 10a ("A plaintiff need not provide evidence of each above-described type."); *id.* at 23a ("[T]he lack of a randomized, controlled experimental study showing that Fixodent causes copper-deficiency myelopathy does not undermine Plaintiffs' experts' inference of causation."). [8] The *Chapman* panel expressed no reservations about the district court's reasoning, and gave no indication that it was

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[8] *See also* Resp. App. 11a (dose-response relationship is "'the single most important factor,'" not a conclusive factor (quoting *McClain*, 401 F.3d at 1242)); *id.* at 16a (analytic epidemiological studies are the "'best evidence,'" not necessary evidence, "of causation" (quoting *Kilpatrick*, 613 F.3d at 1337 n.8)); *id.* at 21a (explaining that a lack of evidence concerning the background risk of myelopathy "is a substantial weakness," not a fatal weakness, "in Plaintiffs' experts' causal reasoning").

affirming the district court judgment on an alternative ground. Instead, after quoting extensively from the district court opinion, *see* Pet. App. 14a-18a, the panel summarized its approval of the district court's analysis in a single paragraph, concluding that "[a]s gatekeeper for the evidence presented to the jury, the judge did not abuse her discretion or commit manifest injustice by precluding . . . Dr. Brewer, Dr. Lautenbach, and Dr. Landolph as experts on general causation," *id.* at 19a.

Given this context, and considering its opinion in its entirety, the *Chapman* panel cannot reasonably be understood as attempting to overrule *sub silentio* an entire line of settled Eleventh Circuit precedent. Nor can the panel's opinion be read as fundamentally disagreeing with the district court's analysis and holding instead (as the Chapmans contend) that an expert's opinion on general causation is inadmissible "as a matter of law" unless based upon epidemiological studies. Pet. 17.

b. The Chapmans fixate on a single paragraph of the panel opinion to contend that the panel adopted a "rigid requirement of epidemiological evidence." *Id.* at 2. However, in stating that the Chapmans' experts exhibited a "lack of knowledge of . . . methodologies this circuit has recognized as indispensable" in prior decisions, Pet. App. 18a, the panel "was not compiling a list of required types of evidence." *Rider*, 295 F.3d at 1202. Instead, consistent with *Rider*, "it was [simply] highlighting the [Chapmans' experts'] failure to present evidence in any of several categories that would have been persuasive." *Id.* at 1203. Likewise, in stating that the experts' "secondary methodologies, including

plausible explanations, generalized case reports, hypotheses, and animal studies are insufficient proof of general causation," Pet. App. 19a, the panel was addressing the particular evidence relied upon by the Chapmans' experts and specifically addressed at length by the district court. *See* Resp. App. 24a-41a. The panel did not hold that the district judge should have ignored this evidence entirely, but only that "the district judge did not abuse her discretion" in finding that such evidence was not enough to allow the Chapmans' general causation experts to testify at a trial. Pet. App. 25a.

Moreover, notwithstanding the Chapmans' repeated assertions to the contrary, *see supra* note 7, the panel clearly did not focus exclusively on their experts' lack of supporting epidemiological studies. At the outset of its analysis, the panel noted *five* different categories of evidence that the district court found entirely lacking: "dose-response relationship, epidemiological evidence, background risk of the disease, physiological processes involved, and clinical studies." Pet. App. 15a. It then summarized and endorsed the district court's analysis as to *three* of those categories of evidence that were lacking: dose-response relationship, *id.* at 15a-16a, epidemiology, *id.* at 16a-17a, and background risk, *id.* at 17a-18a. In short, the Chapmans act as if their experts were barred from testifying solely because they could not tender epidemiological studies to the court, but the reality is that they lacked reliable evidence *of any type* to opine that Fixodent could cause a myelopathy.[9]

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[9] While analytic epidemiological studies may produce evidence of a dose-response relationship or background risk,

At bottom, the Chapmans attempt to manufacture a circuit split by isolating a single paragraph in the panel's opinion and reading it out of context from the rest of the opinion, the district court opinion it affirmed, and prior, binding Eleventh Circuit precedent. This is not a proper method for interpreting judicial opinions. *See St. Mary's Honor Ctr. v. Hicks*, 509 U.S. 502, 518 (1993) (accepting an interpretation of precedent that "creates difficulty with one sentence" instead of one that "causes many portions of the opinion to be incomprehensible or deceptive").

3. In any event, even if the *Chapman* panel opinion could be interpreted (contrary to settled Circuit precedent) as holding that an expert needs epidemiological studies to opine on general causation, that, at most, would interject intra-circuit tension into Eleventh Circuit case law. The Eleventh Circuit will be able, and should be allowed, to clarify any ambiguity regarding the consistency of its own precedents. Indeed, the Eleventh Circuit follows a rule that "[w]here prior panel decisions conflict,

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(continued…)

> dose-response and background risk/prevalence evidence may be developed through various other methods, including clinical studies involving humans or appropriately comparable animals, public health surveys, surveillance data, and DNA or *in vitro* testing (testing at the cellular or molecular level). *See, e.g.*, Goldstein, et al., *Reference Guide on Toxicology*, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 639, 641, Third Ed. ("Reference Manual"); Green, *Reference Guide on Epidemiology*, in Reference Manual 563-65; Mariner, *Medicine and Public Health: Crossing Legal Boundaries*, 10 J. Health Care L. & Pol'y 121, 138 n.76 (2007); *id*. at 141.

[courts] are bound to follow the oldest one." *Crist v. Carnival Corp.*, 410 F. App'x 197, 199 n.1 (11th Cir. 2010) (per curiam). Thus, a future Eleventh Circuit panel would remain bound to follow *Rider*, *Kilpatrick*, *Hendrix* and *Wells*, even if it did agree with the strained reading of the panel opinion advocated by the Chapmans.

B. The Law Of Other Circuits Is In Accord With Eleventh Circuit Precedent.

1. As explained above, the law of the Eleventh Circuit is exactly what the Chapmans urge: "epidemiology is not required to prove causation in a toxic tort case." *Rider*, 295 F.3d at 1199. Accordingly, it does not conflict with case law from the First, Third, Fourth, Ninth, and D.C. Circuits. Indeed, the lead case the Chapmans cite to demonstrate a circuit split—the First Circuit's decision in *Milward v. Acuity Specialty Products Group, Inc.*—cites *Rider* as the only case supporting its holding that "[e]pidemiological studies are not per se required as a condition of admissibility." 639 F.3d at 24 (citing *Rider*, 295 F.3d at 1198, and Restatement (Third) of Torts: Liability for Physical and Emotional Harm § 28 cmt. (c)(3) (2010) (the "Restatement")). The law in the other circuits identified by the Chapmans is to the same effect. In fact, the Chapmans cite the Restatement for the proposition that "[m]any courts find that requiring proof by scientific evidence that does not exist and is not reasonably available to the plaintiff when other, reasonably probative evidence exists is an overbroad method for screening cases," Restatement § 28, reporter's notes to cmt. (c)(3), but they fail to mention that the Restatement cites as support for

this proposition *two Eleventh Circuit decisions* (*Rider* and *Wells*), as well as several district court decisions from within the Eleventh Circuit. *See id.*, reporter's notes to cmt. (c)(3).

Moreover, the Eleventh Circuit has held that "'products liability law does not preclude recovery until a "statistically significant" number of people have been injured or until science has had the time and resources to complete sophisticated laboratory studies of the chemical.'" *Wells*, 788 F.2d at 745 (quoting *Ferebee*, 736 F.2d at 1535-36). Once again, this is consistent with the First, Third, Fourth, Ninth, and D.C. Circuit decisions that the Chapmans quote in their petition. Pet. 20-23.

Finally, the Chapmans also misstate Fifth Circuit law. They contend that "the Fifth Circuit has embraced a rule requiring epidemiological evidence as a prerequisite to the admissibility of an expert's general causation opinion." *Id.* at 26. However, the very case they cite states the opposite: "While *we do not hold that epidemiological proof is a necessary element* in all toxic tort cases, it is certainly a very important element." *Brock v. Merrell Dow Pharma.*, 874 F.2d 307, 313 (5th Cir. 1989) (emphasis added); *see also Wells v. SmithKline Beecham Corp.*, 601 F.3d 375, 380 (5th Cir. 2010) (stating only that "this court has *frowned on* causative conclusions bereft of statistically significant epidemiological support," not holding that such conclusions are categorically inadmissible (emphasis added)).

2. Just as they overstate the rigidity of Fifth and Eleventh Circuit precedent, so too do the Chapmans overstate the leniency of the law in the First, Third, Fourth, Ninth, and D.C. Circuits. Those courts do

not hold that all methodologies and evidence are equal, such that a single flawed case report is entitled to the same weight as large analytical epidemiological studies. To the contrary, like the Fifth and Eleventh Circuits, other circuits expressly recognize that the absence of certain forms of evidence—such as epidemiological studies and dose-response relationship data—is significant in evaluating whether an expert can reliably opine on general causation. For example, in a case cited by the Chapmans, the D.C. Circuit explained that "testing [ ] case reports through epidemiological studies—the methodology that calls for checking controlled population studies to see if they confirm the hypotheses suggested in individual case reports—is an important scientific approach." *Meister v. Med. Eng'g Corp.*, 267 F.3d 1123, 1127 (D.C. Cir. 2001) (internal quotation marks omitted). And the Fourth Circuit has been clear that "[s]howing a dose-response relationship"—which the Chapmans' experts wholly lacked—is "an important factor in establishing causation." *Newman v. Motorola, Inc.*, 78 F. App'x 292, 294 (4th Cir. 2003) (affirming exclusion of expert opinion in part because expert failed to show such a relationship); *see also Zellers v. NexTech N.E., LLC*, 533 F. App'x 192, 198 (4th Cir. 2013) (per curiam) (holding "that a 'plaintiff must demonstrate the levels of exposure that are hazardous to human beings generally as well as the plaintiff's actual level of exposure'" (quoting *Westberry v. Gislaaved Gummi AB*, 178 F.3d 257, 263 (4th Cir. 1999) (emphasis added)).

In sum, all of the circuits discussed in the petition give a consistent answer to the Question Presented—"while epidemiological studies may be powerful

evidence of causation, the lack thereof is not fatal to a plaintiff's case." *Rider*, 295 F.3d at 1198.

II. THIS CASE IS A POOR VEHICLE IN WHICH TO ADDRESS THE QUESTION PRESENTED IN THE PETITION.

Putting aside the fact that the Chapmans' alleged circuit split does not exist, this case is a poor vehicle for considering their Question Presented. First, both the district court and the panel held that, in addition to failing to present admissible evidence of *general* causation, the Chapmans also failed to present admissible evidence of *specific* causation. Because this is an independent ground upon which the panel affirmed the district court, this Court's resolution of the Question Presented—which addresses only general causation—cannot affect the outcome of this case. Second, the Chapmans have not identified any legal error in the district court opinion, which accepted (in accord with Eleventh Circuit precedent and the rule advocated by the Chapmans) that their experts were not required to rely on epidemiological studies as a precondition of admissibility. For this additional reason, a decision by this Court affirming or rejecting such a precondition would not alter the district court's judgment.

A. The Chapmans Do Not Challenge An Independent Ground Of The Decisions Below.

In addition to holding that the Chapmans lacked admissible evidence on general causation, the district court held that they had *also* failed to present admissible evidence of specific causation—namely, that Marianne Chapman's myelopathy was caused by her use of Fixodent. Resp. App. 41a-46a.

The *Chapman* panel affirmed that conclusion. Pet. App. 19a-25a. This is an independent basis for the exclusion of the Chapmans' expert testimony on general causation, since that testimony (that Fixodent can cause myelopathy) would be irrelevant (and unduly prejudicial) if the Chapmans could not connect such evidence to the facts of their case. *See Gen. Elec. Co.*, 522 U.S. at 146 (expert testimony must be "connected" to facts of the case); *Daubert*, 509 U.S. at 591-92 (holding that Rule 702 "requires a valid scientific connection to the pertinent inquiry as a precondition to admissibility"). Moreover, the exclusion of the Chapmans' specific-causation evidence is an independent ground for affirming the district court's grant of summary judgment, because the Chapmans would have needed admissible evidence of general *and* specific causation to survive summary judgment. *See, e.g.*, *McClain*, 401 F.3d at 1239 (specific causation must be proved, even when general causation is assumed); *Guinn v. AstraZeneca Pharm. LP*, 602 F.3d 1245, 1256 (11th Cir. 2010) (holding that summary judgment was appropriate where the plaintiff had failed to present admissible evidence of specific causation).

The Chapmans contend that the *only* reason the panel affirmed the exclusion of their evidence on specific causation is that Dr. Greenberg, in his differential diagnosis, "ruled-in" Fixodent as a potential cause of Ms. Chapman's myelopathy even though that connection was not supported by admissible general causation expert testimony. Pet. 18, 34. This, however, misreads the panel decision.

The *Chapman* panel agreed with the district court that "Dr. Greenberg did not follow" a reliable

methodology for differential diagnosis in several ways. Pet. App. 20a. While noting the district court's conclusion that Dr. Greenberg's analysis was not reliable because he "ruled-in" "Fixodent-induced copper-deficiency myelopathy" as a cause of Ms. Chapman's disease, *id.* at 25a, the panel also explained that "Dr. Greenberg failed to explore fully other potential causes of Marianne Chapman's [myelopathy]," *id.* at 22a. In particular, the panel held that Dr. Greenberg's analysis was unreliable because he "failed to consider obvious alternative causes for [Ms.] Chapman's CDM, such as hereditary and acquired conditions known to cause myelopathies," *id.* at 24a; "provided no support for his hypothesis that [Ms.] Chapman's anemia, neutropenia, and myelopathy resulted from a single cause rather than several causes," *id.*; and "omitted consideration of idiopathic causes for [Ms.] Chapman's CDM," *id.* Thus, the panel concluded that Dr. Greenberg's differential diagnosis was unreliable both because he considered Fixodent as a potential cause of Ms. Chapman's myelopathy without sufficient support *and* because he did not consider "numerous [other] potential causes" for Ms. Chapman's myelopathy. *Id.* at 25a.

Again, the panel's analysis tracks that of the district court, which determined that Dr. Greenberg's differential diagnosis was inadmissible for two separate reasons: Dr. Greenberg "ruled-in and considered an etiology—Fixodent-induced copper-deficiency myelopathy—that has not been established to cause Ms. Chapman's disease" *and* he "did not rule-in all possible causes before he started ruling things out." Resp. App. 43a. "For *these reasons*," the district court held, "Dr. Greenberg did

not perform a reliable differential diagnosis," thereby necessitating that his "testimony on specific causation be excluded." *Id*. at 46a (emphasis added).

In light of the district court and panel's specific causation rulings, this Court's analysis of the Question Presented, concerning only general causation, would be entirely academic in the context of this case. However this Court resolved that question, summary judgment still would be warranted because there was no admissible expert testimony that Ms. Chapman's myelopathy was caused by Fixodent.

B. The District Court Decision Does Not Implicate The Claimed Circuit Split.

Even as to general causation, this case does not implicate the Question Presented. Whatever possible ambiguity might exist in the *Chapman* panel opinion, the district court clearly and expressly held that the Chapmans' experts were not required to present any particular type of evidence. *See supra* at 22-23 and note 5. Having done so, it went on to consider *all* of the methodologies and categories of evidence relied upon by the Chapmans' general-causation experts, and concluded that *none* of them rendered the experts' opinions sufficiently reliable. Resp. App. 24a-41a. Adopting the rule urged here by the Chapmans would change neither the result, nor even the reasoning, of the district court in excluding their general causation experts. Thus, once again, this Court's consideration of the Question Presented would be entirely academic in this case.

III. THE DECISIONS BELOW WERE CORRECT.

The district court correctly excluded the Chapmans' expert opinion testimony on general

causation, and the Eleventh Circuit panel correctly concluded that this ruling was not an abuse of discretion. Indeed, the decisions of these courts are in line with several other courts, all of which have held that purported expert opinions of a causal link between Fixodent and myelopathy are simply too unreliable to be admitted into evidence. *See In re Denture Adhesive Cream Litig.*, 2014 Phila. Ct. Com. Pl. LEXIS 135; *Jacoby*, 2013 Pa. Super. LEXIS 5563; *Adams*, 2014 Ohio Misc. LEXIS 3.

Under *Daubert*, district courts perform an important "gatekeeping" function in "ensuring that an expert's testimony both rests on a reliable foundation and is relevant to the task at hand." 509 U.S. at 597. Courts "must resolve disputes finally and quickly." *Id.* Thus, while "[c]onjectures that are probably wrong" can be valuable to the scientific process, they "are of little use . . . in the project of reaching a quick, final, and binding legal judgment – often of great consequence—about a particular set of events in the past." *Id.* And though "a gatekeeping role for the judge" may on occasion lead to the exclusion of "authentic insights," that "is the balance that is struck by Rules of Evidence designed not for the exhaustive search for cosmic understanding but for the particularized resolution of legal disputes." *Id.*

In this case, the district court properly performed its gatekeeping function. *None* of the Chapmans' experts on general causation employed *any* of the methodologies typically found to be reliable for establishing general causation in a toxic tort case. No expert could demonstrate a dose-response relationship. Resp. App. 10a-15a. No expert could

present analytic epidemiological studies in support of his theory. *Id.* at 16a-18a, 22a-23a. And no expert could quantify the prevalence of CDM in the general population or identify any greater risk Fixodent users faced of developing CDM. *Id.* at 18a-21a.[10]

Instead, the Chapmans' experts relied heavily on anecdotal case reports, which are by definition merely observations of a single patient or a small number of patients. *Id.* at 28a-29a. And the primary case reports upon which they relied contained numerous inaccuracies and methodological flaws *confirmed by the very authors of those case reports*. *Id.* at 30a. Because of this, the district court properly concluded that the Chapmans' experts could not reliably opine that Fixodent can cause myelopathy, and the *Chapman* panel correctly determined that this conclusion was well within the district court's discretion.

CONCLUSION

For the foregoing reasons, the petition for a writ of certiorari should be denied.

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[10] The experts also could not establish the physiological mechanism by which Fixodent (at the start of the supposed causal chain), or even copper deficiency (several links down the chain), allegedly leads to myelopathy. Resp. App. 21a-22a.

Respectfully submitted,

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APPENDIX

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA
MIAMI DIVISION

Case No. 09-2051-MD-ALTONAGA

In re

DENTURE CREAM PRODUCTS LIABILITY LITIGATION.
_____/

This Document Relates to Case No. 9:09-CV-80625-CMA
(*Chapman, et al. v. Procter & Gamble Distributing LLC*)

ORDER

THIS CAUSE came before the Court on Defendant, the Procter & Gamble Distributing LLC's ("Procter & Gamble['s]") motions to exclude all or part of the testimony of seven of Plaintiff, Marianne Chapmans' expert witnesses. (*See* [ECF Nos. 1040–1044]). The proposed testimony covers a variety of topics. The majority of the discussion in this Order focuses on the Motion to Exclude the Opinions of Plaintiffs' Experts Drs. Brewer, Greenberg, and Landolph ("Brewer Motion") [ECF No. 1040], and the Motion to Exclude the Opinions of Plaintiffs' Expert Dr. Ebbing Lautenbach ("Lautenbach Motion") [ECF No. 1041], each filed on April 1, 2011.[1] The proposed

[1] Dr. Brewer is Plaintiffs' expert on zinc metabolism, Dr. Landolph is a toxicologist, and Dr. Lautenbach is an epidemiologist.

testimony of Drs. Brewer, Landolph, and Lautenbach concerns whether Fixodent is, in general,[2] capable of causing a copper-deficiency myelopathy;[3] while Dr. Greenberg's proposed testimony addresses the specific question of whether Plaintiff, Marianne Chapman's myelopathy was caused by her use of Fixodent.[4] The Court has carefully considered the

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In other motions, Defendant also seeks to exclude the testimony of Dr. Frederick Raffa ("Raffa Motion") [ECF No. 1042], portions of the testimony of Dr. J. Anthony Von Fraunhofer ("Fraunhofer Motion") [ECF No. 1043], and the testimony of Dr. Michael S. Wogalter ("Wogalter Motion") [ECF No. 1044], all filed on April 1, 2011. Defendant does not challenge the Report (*see* ECF No. 1072-14]) of Dr. Prohaska, Plaintiffs' biochemist, linking copper deficiency and blood disorders.

[2] "'General causation is concerned with whether an agent increases the incidence of disease in a group and not whether the agent caused any given individual's disease.'" *McClain v. Metabolife, Int'l., Inc.*, 401 F.3d 1233, 1239 (11th Cir. 2005) (quoting Michael D. Green *et al.*, *Reference Guide on Epidemiology*, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 392 (Federal Judicial Center, 2d ed. 2000) [hereinafter Green, REFERENCE MANUAL])).

[3] A number of different terms have been used — more or less as synonyms, regardless whether that is medically accurate — in the course of the litigation to refer to a constellation of neurological injuries allegedly caused by long-term use of Fixodent. Those terms include myelopathy, myeloneuropathy, myelopolyneuropathy, copper-deficiency myelopathy, peripheral neuropathy, CNS demyelination, axonal polyneuropathy, and others.

[4] Dr. Von Fraunhofer, a dental technologist, also makes the link between Fixodent and myelopathy (*see* Von Fraunhofer Rep. [ECF No. 1046-5]), but he is not a primary witness on general causation. Dr. Von Fraunhofer bases his causation conclusion on two case reports. (*See* Von Fraunhofer Rep. 15 (citing Nations *et al., Denture cream: An unusual source of excess zinc, leading to*

Motions; the thousands of pages of filings by the parties, including the experts' reports and depositions, and scientific literature; as well as oral argument by the parties, a broad variety of secondary literature on the use of scientific evidence in the courtroom, and the law.

I. BACKGROUND

Thirty-three year old Marianne Chapman suffers from a constellation of neurological symptoms that evolved during a 2.5 year period from April 2006 to January 2009. (*See* Greenberg Rep. 4 [ECF No. 1047-1]). These symptoms began in 2006 when she developed a numbness in her fingertips, followed a month later by numbness in both feet.[5] (*See id.*). Eventually, "all feeling in the hands and feet were lost, pins and needles parasthesis were [sic] present, and pain with light touch in the feet was prominent." (*Id.*). From June 2006 to January 2008, Ms. Chapman developed a progressive gait ataxia, which first caused her to trip frequently while walking in the dark, and then kept her confined to bed for fear of falling while walking. (*See id.*). A

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hypocupremia and neurologic disease, NEUROLOGY, 71:639-643 (June 2008) (the "Nations Article"), and Hedera et al., *Myelopolyneuropathy and pancytopenia due to copper deficiency and high zinc levels of unknown origin II,* NEUROTOXICOLOGY (2009) (the "Hedera Article"). As will become apparent, the basis of his general causation inference is subject to the same reliability concerns as arise with Drs. Brewer, Landolph, and Lautenbach.

[5] Dr. Greenberg notes, but considers unrelated, a March 2004 visit to the doctor, at which Ms. Chapman complained of numbness along the right lateral leg. She was discovered to have a vitamin B12 deficiency, was treated for that deficiency, and the leg numbness resolved. (*See* Greenberg Rep. 4).

burning pain in her hands and feet intensified during this period and required management with opiods. (*See id.*). In July 2006, she was discovered to have blood dyscrasias, including anemia and neutropenia (low red and white blood cell counts). (*See id.*). Around January 2008, Ms. Chapman developed "subacute bilateral asymmetric wrist and finger drop," which intensified in both hands over a several-month period and limited her ability to extend her fingers and thumbs. (*Id.*).

Plaintiffs contend Ms. Chapman's symptoms are the result of zinc-induced copper-deficiency myelopathy brought on by her use of two to four 68-gram tubes[6] of Fixodent denture adhesive every week for eight years to hold her dentures in place. (*See* Brewer Opp'n [ECF No. 1071]; *see also* Greenberg Rep. 8). In contrast, Procter & Gamble maintains the methodologies used by Plaintiffs' experts to conclude that Fixodent can cause myelopathy and that Fixodent caused Ms. Chapman's neurological problems are unreliable, and thus the experts' testimony should not be admitted.

After Defendant filed its *Daubert* motions, additional deposition testimony was taken from the experts. The Defendant was then permitted to supplement its *Daubert* motions based on those depositions. (*See* [ECF No. 1037]). Plaintiffs were permitted to respond to those supplemental briefs.

II. LEGAL STANDARD

Federal Rule of Evidence 702, which governs expert testimony, states as follows:

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[6] The 68-gram tube is about the size of a medium-sized tube of toothpaste.

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

Rule 702 requires district courts to ensure "that an expert's testimony both rests on a reliable foundation and is relevant to the task at hand." *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 597 (1993). This "gatekeeping" function must be performed with regard to the admissibility of both expert scientific evidence and expert technical evidence. *See United States v. Frazier*, 387 F.3d 1244, 1260 (11th Cir. 2004) (citing *Daubert*, 509 U.S. at 589 n.7 & 597; *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 147 (1999)). "This function inherently requires the trial court to conduct an exacting analysis of the *foundations* of expert opinions to ensure they meet the standards for admissibility under Rule 702." *Id.* (alterations and internal quotation marks omitted).

In determining the admissibility of expert testimony, the Eleventh Circuit requires district courts to conduct a three-part inquiry about whether:

> (1) the expert is qualified to testify competently regarding the matters he intends to address; (2) the methodology by which the expert reaches his conclusions is sufficiently reliable as

> determined by the sort of inquiry mandated in *Daubert*; and (3) the testimony assists the trier of fact, through the applications of scientific, technical, or specialized expertise, to understand the evidence or to determine a fact in issue.

Hendrix ex rel. G.P. v. Evenflo Co., 609 F.3d 1183, 1194 (11th Cir. 2010) (citing *Frazier*, 387 F.3d at 1260). The burden is on the proponent of the expert testimony to show, by a preponderance of the evidence, that the testimony satisfies each prong. *See id.* (citing *Boca Raton Cmty. Hosp., Inc. v. Tenet Health Care*, 582 F.3d 1227, 1232 (11th Cir. 2009)). In this case, as in *Hendrix*, only the second prong — reliability — is in dispute. *See id.*

In *Daubert*, the Supreme Court suggested a non-exhaustive list of several factors to consider in determining if a specific methodology is reliable under Rule 702: whether the methodology can and has been tested; whether the methodology has been subjected to peer review and publication; the known or potential rate of error and the existence and maintenance of standards controlling operation of the methodology; and whether the methodology has gained general acceptance in the scientific community. *See Daubert*, 509 U.S. at 593–94 (declining to set forth a "definitive checklist or test"); *accord Kumho*, 526 U.S. at 141. In *Kumho*, the Supreme Court emphasized, "the trial judge must have considerable leeway in deciding in a particular case how to go about determining whether particular expert testimony is reliable." *Kumho*, 526 U.S. at 152. Nevertheless, while the inquiry is "a flexible one," the focus "must be solely on principles and methodology, not on the conclusions that they

generate." *Daubert*, 509 U.S. at 594–95. "But conclusions and methodology are not entirely distinct from one another . . . [and] nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997). "Rather, the trial court is free to 'conclude that there is simply too great an analytical gap between the data and the opinion proffered.'" *Hendrix*, 609 F.3d at 1194 (citing *Joiner*, 522 U.S. at 146).

III. ANALYSIS

Doctors Brewer, Landolph, and Lautenbach, each to a greater or lesser extent and despite coming from different disciplines, rely on the same information, predominantly case studies, to conclude the use of very large amounts of Fixodent over a very long period of time can cause a class of neurological diseases called myelopathy.[7] Because Drs. Brewer, Landolph, and Lautenbach use the same information to infer general causation, the Court addresses the admissibility of their proposed testimony together in section III.A of this Opinion. In section III.B, the Court addresses the testimony of Dr. Greenberg, Plaintiffs' expert on specific causation, who concludes it was Marianne Chapman's use of Fixodent that caused her to develop zinc-induced copper-deficiency myelopathy. In section III.C, the Court addresses

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[7] A myelopathy is any "disturbance or disease of the spinal cord." THE AMERICAN HERITAGE MEDICAL DICTIONARY (Houghton Mifflin 2007); (*see also* Greenberg Dep. 23:8-9 [ECF No. 1137-3] ("Myelopathy is a category of conditions that affect the spinal cord.")).

Defendant's motions to exclude the testimony of Drs. Wogalter, Von Fraunhofer, and Raffa.

A. General Causation: Whether Plaintiffs' Experts Use a Reliable Scientific Methodology to Conclude Fixodent Can Cause a Myelopathy.

In *McClain*, the Eleventh Circuit noted "toxic tort cases usually come in two broad categories: first, those cases in which the medical community generally recognizes the toxicity of the drug or chemical at issue, and second, those cases in which the medical community does not generally recognize the agent as both toxic and causing the injury plaintiff alleges."[8] *McClain*, 401 F.3d at 1239. Not surprisingly, the parties dispute the proper categorization of the agent[9] in this case; however, for reasons that are explored in great detail below, this case falls into the second category because there is no reliable basis to conclude either Fixodent or zinc can cause copper-deficiency myelopathy.

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[8] Some examples of known toxic agents that the Eleventh Circuit highlights are "asbestos, which causes asbestosis and mesothelioma; silica, which causes silicosis; and cigarette smoke, which causes cancer." *McClain*, 401 F.3d at 1239. The alleged association between the zinc in Fixodent and copper-deficiency myelopathy does not have the same widespread acceptance by the medical community as the Eleventh Circuit's examples.

[9] The categorization is complicated because the parties disagree about what the agent or chemical at issue is. It is Plaintiffs' view that they need only show that zinc can cause copper-deficiency myelopathy and that Fixodent contains absorbable zinc, while Defendant argues Plaintiffs must show that Fixodent can cause a copper-deficiency myelopathy.

Plaintiffs submit the testimony of three experts — Drs. Brewer, Landolph, and Lautenbach — in an attempt to establish that Fixodent is capable of causing a myelopathy. Dr. Brewer would testify "that zinc containing Fixodent denture adhesives are a health hazard and capable of causing severe hematological and neurological injury." (Brewer Rep. [ECF No. 1046-1]). Dr. Landolph would testify "that long-term use of Fixodent (containing 1.69% zinc) will result in . . . neurotoxic, neurologic, and hematologic consequences." (Landolph Rep. [ECF No. 1046-7]). Dr. Lautenbach, whose opinion is expressed in a rebuttal report, would testify, somewhat tepidly, that there is "an association between Fixodent and myeloneuropathy" and he would "consider the myeloneuropathy as a 'probable' reaction related to denture adhesive use." (Lautenbach Rep. ¶¶ 40, 45 [ECF No. 1046-9]).[10]

1. Reliable Methodologies

A survey of Eleventh Circuit *Daubert* jurisprudence in toxic-tort cases identifies several types of evidence and methodologies that have been described as reliable bases for an inference of general causation. Those types of evidence and methodologies are drawn from toxicology and epidemiology and include the dose-response

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[10] Dr. Greenberg would testify, "[b]etween 2007–2009, several publications established that zinc poisoning from certain denture adhesive creams are the most comm on cause of copper-deficiency myelopathy." (Greenberg Rep. 1 (referencing five case-report articles)). He relies heavily on the Hedera Article. (*See id*. ("[O]ne research group re-interviewed their previous 11 patients with elevated zinc levels and copper deficiency and discovered that all 11 were denture cream users.")).

relationship,[11] epidemiological studies,[12] the amount of background risk of the disease,[13] an understanding of the physiological mechanisms involved, and clinical studies or tests. *See* Green, REFERENCE MANUAL 374–379. A plaintiff need not provide evidence of each above-described type, but an inference of general causation that is made in the absence of any of these preferred types of evidence has been and will be deemed unreliable in this Circuit.

a. Dose-Response

"All substances are poisonous — there is none which is not; the dose differentiates a poison from a remedy." David Eaton, *Scientific Judgment and Toxic Torts: A Primer in Toxicology for Judges and*

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[11] The dose-response relationship is "[a] relationship in which a change in amount, intensity, or duration of exposure to an agent is associated with a change — either an increase or decrease — in risk of disease." *McClain*, 401 F.3d at 1241–42 (citing Green, REFERENCE MANUAL 390). "The expert who avoids or neglects [the dose-response] principle of toxic torts without justification casts suspicion on the reliability of his methodology." *Id.* at 1242.

[12] Epidemiology, a field that concerns itself with finding the causal nexus between external factors and disease, is generally considered to be the best evidence of causation in toxic tort actions.'" *Kilpatrick v. Breg, Inc.*, 613 F.3d 1329, 1337 n.8 (11th Cir. 2010) (quoting *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1198 (11th Cir. 2002)).

[13] Background risk is "[t]he risk a plaintiff and other members of the general public have of suffering the disease or injury that the plaintiff alleges *without* exposure to the drug or chemical in question." *McClain*, 401 F.3d at 1242 (alteration and emphasis in original). "A reliable methodology should take into account the background risk." *Kilpatrick*, 613 F.3d at 1342 (quoting *McClain*, 401 F.3d at 1243–44).

Lawyers, 12 J.L. & POL'Y 1, 11 (2003) [hereinafter Eaton] (quoting CASARETT AND DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS Chs. 1, 4 (McGraw Hill 6th ed. 2001) (quoting the 16th Swiss-German Physician/Philosopher Paracelsus)). Because all substances have the potential to be toxic, "'the relationship between dose and effect (dose-response relationship) is the hallmark of basic toxicology,'" *McClain*, 401 F.3d at 1242 (quoting Eaton 15), and "'is the single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect'" *id*. (quoting Eaton 11). "'[F]or most types of dose-response relationships following chronic (repeated) exposure, thresholds exist, such that there is some dose below which even repeated, long-term exposure would not cause an effect in any individual.'" *Id*. (quoting Eaton 16). Often "'low dose exposures — even for many years — will have no consequence at all, since the body is often able to completely detoxify low doses before they do any damage.'" *Id*. (quoting Green 13). This last statement is almost certainly true of Fixodent, which, as even Plaintiffs seem to concede, is safe when used in moderate amounts. (*See* Hr'g Tr. 134:9–135:24).

Nevertheless, Fixodent and the zinc it contains, like water and oxygen,[14] are potentially toxic. Common sense suggests that one would expect consuming three-fifths of a pound[15] of denture cream

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[14] *See*, *e.g.*, D J Farrell *et al., Fatal water intoxication*, 56(10) J. CLIN. PATHOL. 803 (2003); C. Acott, *Oxygen Toxicity: A brief history of oxygen in diving*, 29(3) S. PAC. UNDERWATER MED. SOC. 150 (1999).

[15] Four 68-gram tubes of Fixodent are roughly equal to .6 pounds of Fixodent.

per week for eight years would have some type of negative consequence. "Thus, the question for causation purposes is: At what levels of exposure do what kinds of harm occur?" *Cavallo v. Star Enter.*, 892 F. Supp. 756, 769 n.27 (E.D. Va. 1995), *rev'd on other grounds, Cavallo v. Star Enter.*, 100 F.3d 1150, 1157–59 (4th Cir. 1996). In this case, Plaintiffs' experts contend the use of Fixodent in a particular way causes a particular disease — specifically, Plaintiffs' experts conclude extremely large amounts of Fixodent applied to dentures several times a day for a period of many years can cause copper-deficiency myelopathy.

Yet, neither Plaintiffs' experts nor the articles on which they rely determine how much Fixodent must be used for how long to increase the risk of a copper-deficiency, or for how long a copper-deficiency must persist before an individual is at an increased risk of developing a myelopathy.[16] Plaintiffs argue

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[16] Dr. Brewer:

> Q. Have you ever determined the dose of Fixodent necessary to consistently place individuals into a negative copper balance?
>
> A. Experimentally, no.

(Brewer Dep. 108:8–11 [ECF Nos. 1087-1, 1137-4]; *see also id.* 109:10–12, 177:14–18).

* * *

> Q. But you're unable to tell us how long it has to be that low to cause myelopolyneuropathies or myelopathies?
>
> A. Yeah. I can tell you that it will not happen in the first couple of weeks.
>
> Q. Okay.
>
> A. But I don't know how long it takes to happen.

Dr. Brewer's Wilson's disease[17] research establishes some people are placed into a negative copper balance with a single 25 mg dose of zinc. (*See* Brewer Opp'n 10). While this may be true, there is a large analytical gap between the proposition that a 25 mg dose of zinc may, at a given time, place a particular person into a temporary negative copper balance, to the proposition that some people who ingest 25 mg of zinc per day for many years will develop a severe copper deficiency with neurological symptoms. Dr. Brewer's Wilson's disease experiments do establish what dose of Galzin, or zinc acetate, is necessary to induce a negative copper balance (*see*

(*Id*. 60:1–8).

Dr. Lautenbach:

Q. Now, do you know how much below normal copper has to be, serum copper has to be and for how long before you have myelopathies?

A. I don't know.

(Lautenbach Dep. 62:5–9 [ECF No. 1137-1]).

Dr. Landolph:

Q. So no studies have been done to determine how low the copper must be in the serum and for how long to cause myelopathy?

A. I had not seen such a precise curve . . . .

(Landolph Dep. 43:3-8 [ECF No. 1087-2]).

Hedera Article: "We could only estimate daily zinc exposure . . . [because] the bioavailability of zinc from denture cream is unknown." (Hedera Article 2; *see also* Hedera Dep. 263:11–14 [ECF No. 1137-6] ("I don't have a good date to how long does it take to — to — to develop problems; so we didn't go into such details.")).

[17] In Wilson's disease there is too much copper in the body's tissues.

Brewer Rep. 4); however, the Procter & Gamble pharmacokinetic studies indicate that the zinc in Fixodent is less bio-available than that in zinc acetate. (*See* PK Study 35 [ECF No. 1072-1]).[18]

Moreover, one cannot simply figure out the dose of zinc from Fixodent by doing some simple arithmetic[19] based on the pharmacokinetic studies because, apparently to the surprise of the investigators in that study, a 6 g dose of Fixodent only delivered slightly more bio-available zinc than the 3 g dose. (*See* PK Study 35) ("[S]ystemic exposures from Fixodent 6 g were not markedly greater than Fixodent 3 g even though the 6 g product had twice the amount of elemental zinc (100 mg versus 50 mg) relative to the 3 g product."). This suggests taking more and more Fixodent may not expose someone to more and more

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[18] Dr. Brewer also acknowledged this:

> Q. Exposure to a polymer matrix does not equate to exposure to the individual components of the polymer matrix, does it?
>
> A. Are you referring to oral ingestion of such?
>
> Q. Yep.
>
> A. In that case, no, it doesn't. They don't correspond directly.

(Brewer Dep. 78:13–20).

[19] Plaintiffs disagree:

> We know, even based on their numbers in the pharmacokinetic study that there is a relative bioavailability of the zinc in Fixodent compared to the 25 milligram zinc acetate supplement. So we can *easily make a ready comparison*, as Dr. Landolph did, the toxicologist, and show she was consuming huge amounts of zinc.

(Hr'g Tr. 93:14–19) (emphasis added).

zinc; that is, there may be some limiting factor due to the composition of Fixodent, human biology, or something else.[20]

For these reasons, one cannot reliably infer from Dr. Brewer's Galzin studies how much Fixodent is necessary to consistently induce a negative copper balance. Accordingly, there is no dose-response evidence which Plaintiffs' experts may use to reliably infer what type of exposure level to Fixodent is necessary to induce a negative copper balance, to cause a copper deficiency, or to cause a myelopathy.

b. Epidemiological Evidence and Methodologies

"Epidemiologic evidence identifies agents that are associated with an increased risk of disease in groups of individuals, quantifies the amount of excess disease that is associated with an agent, and provides a profile of the type of individual who is likely to contract a disease after being exposed to an agent." Green, REFERENCE MANUAL 336. There are two classes of epidemiological evidence: analytical and descriptive. (*See* Lautenbach Rep. ¶ 42). Analytical

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[20] Another hole in the dose-response picture is that, with the exception of the primogenital case report of a man who was eating pellets of Poligrip, most of the case-study subjects and Ms. Chapman applied denture cream to their dentures in very large amounts but for its intended purpose — to hold their dentures in place. Some of the excess would ooze out immediately and some of the remainder would wash out or be swallowed with food between applications. In order to obtain a reliable understanding of Fixodent's actual effect on copper balance, the product's actual usage patterns should be modeled in tests to determine if it is capable of delivering zinc in a way that will cause a negative copper balance and, within ethical limits, a copper deficiency.

evidence consists of experimental and observational studies, while descriptive evidence consists of case studies and case series. (*See id*.). The first type of analytical evidence, experimental studies, is discussed separately below. The second type, observational studies, includes case-control studies, cohort studies, cross-sectional studies, and ecological studies. (*See id*.); *see also* Green, REFERENCE MANUAL 339. Analytical studies, such as case-control studies and cohort studies, allow the investigator to determine the rates of disease in exposed and unexposed groups. *See* Green, REFERENCE MANUAL 338. This allows calculation of the increased risk of disease attributable to exposure to the agent. *See id*. 348.

Epidemiology is the "best evidence of causation in toxic tort cases." *Kilpatrick*, 613 F.3d at 1337 n.8 (citation omitted); (*see also* Lautenbach Rep. ¶ 42 ("Analytic studies are most rigorous in identifying the determinants of a disease.")). Plaintiffs' experts have no analytical epidemiological evidence on which to base their inference of causation.[21] (*See* Lautenbach Rep. ¶20 ("[N]o analytic epidemiological studies exist to support or refute the association between Fixodent use and myeloneuropathy.")). Instead, Plaintiffs point to Dr. Lautenbach's testimony that analytical

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[21] Dr. Lautenbach:

> Q. To the best of your knowledge, there are no controlled population-based epidemiologic studies testing whether there is an association between denture adhesive and the development of hematologic or neurologic disease. Correct?
>
> A. That's correct.

(Lautenbach Dep. 28:19-25).

epidemiological evidence is not necessary to infer causation when one has enough descriptive epidemiological evidence, like case studies, and a plausible biological explanation. (*See id.* ¶¶ 42–45).

The Eleventh Circuit, although it has not has not completely excluded the possibility that causation may be established by case studies, has been very hostile when experts have relied on them to infer causation. *See McClain*, 401 F.3d at 1254 ("[Case reports] may support other proof of causation.") Indeed, like Dr. Lautenbach, some have argued that "despite . . . limitations, sometimes case reports can contribute to or be very good evidence of causation on their own." CARL F. CRANOR, TOXIC TORTS, SCIENCE, LAW, AND THE POSSIBILITY OF JUSTICE 116 (Cambridge 2006) [hereinafter CRANOR]. But "what makes case studies good evidence about causation is the analysis to which they are subjected and how scientists reason about them." *Id.* 115. Therefore, in the appropriate case, case studies may provide reliable evidence of causation. *But see Haggerty v. Upjohn Co.*, 950 F. Supp. 1160, 1165 (S.D. Fla. 1996) ("[C]ase reports may provide anecdotal support, [but] they are no substitute for a scientifically designed and conducted inquiry.") (citing *Casey v. Ohio Medical Products*, 877 F. Supp. 1380, 1385 (N.D. Cal. 1995)).

As discussed below, this is not an appropriate instance to rely on case studies because the case studies Plaintiffs' experts rely on suffer from a number of inaccuracies and methodological weaknesses that undermine their evidentiary value. There are also a number of problems with Plaintiffs' assertion that there is a plausible biological mechanism — Fixodent-induced copper-deficiency

myelopathy; those weaknesses are also addressed below. Thus, while it is true Plaintiffs' experts, Dr. Lautenbach in particular, use a recognized epidemiological methodology, they have not done so with the degree of intellectual rigor characterized by practitioners in the field.

c. Background Risk of Disease

An important aspect of epidemiological reasoning is knowledge of background risk. Background risk of disease "is the risk a plaintiff and other members of the general public have of suffering the disease or injury that plaintiff alleges *without* exposure to the drug or chemical in question." *McClain*, 401 F.3d at 1243 (emphasis in original); *see also* Green, REFERENCE MANUAL 388. Because epidemiology aims to identify "agents that are associated with an increased risk of disease," Green, REFERENCE MANUAL at 336, one must know the background prevalence of a disease before one can determine if exposure to an agent has increased the risk of that disease. Thus, "[a] reliable methodolgy should take into account the background risk." *McClain*, 401 F.3d at 1243. Plaintiffs' causation experts uniformly testified that they did not know the background risk of copper-deficiency myelopathy.[22] This is a serious

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[22] Dr. Brewer:

> Q. Do you know the incidence of myeloneuropathies in the United States?
>
> A. No.
>
> Q. Do you know the incidence of myeloneuropathies, myelopathies, or myeloneuropathies [sic] among uses of zinc-containing denture adhesives in the United States?

methodological deficiency,[23] which is evident in Dr. Landolph's reasoning:

> Q. What is the incidence of myeloneuropathy in the general population in the United States? . .

> A. No.

(Brewer Dep. 73:2–9).

> Dr. Lautenbach:
>
> Q. Do you know what the incidence of myelopathy is in the general population?
>
> A. I don't. I'm not sure it's been well defined.

(Lautenbach Dep. 25:16–21).

> Dr. Landolph:
>
> Q. You are unable to give me a number setting forth the incidence of myeloneuropathy among users of zinc containing denture adhesives in the United states, correct?
>
> A. That's correct, the precise number, I don't have that data.

(Landolph Dep. 11:14–19).

> Dr. Greenberg:
>
> Q. Do you know what the general incidence – excuse me. Do you know what the incidence of myelopathies is in the general population in the United States?
>
> A. No.
>
> Q. Do you know what the general incidence of myelopathy is in denture adhesive users in the United States?
>
> A. No.

(Greenberg Dep. 28:7–15).

[23] There is also nothing in the experts' reports or testimony about the background risk of hyperzincemia or copper deficiency.

> A. . . . . It seems to be not incredibly common. I don't know the exact number[, but] . . . it seems to be sufficiently common, it being copper deficient myeloneuropathy among denture adhesive wearers that it's provoking the interest of the scientific and medical community to study at this further[. S]o the background is sufficiently low that when they are getting this now in addition to other causes they are beginning to identify that the sufferers, the patients have frequently used denture adhesives containing zinc, so the reports are becoming more frequent with time.

(Landolph Dep. 37:25–38:13).

This is not even good lay reasoning, much less reliable scientific reasoning.[24] Obviously, one cannot infer that denture cream increases the risk of a myelopathy merely from the scientific community's decision to study the question, and one cannot assume the authors of case reports know the background rate of the disease they are studying (especially here, when we have some of those scientists' testimony to the contrary). Moreover, the question of background risk is important because it could be coincidence that any particular denture-cream user has a myelopathy or copper-deficiency

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[24] "The adjective 'scientific' implies a grounding in the methods and procedures of science. Similarly, the word 'knowledge' connotes more than subjective belief or unsupported speculation." *Daubert*, 509 U.S. at 590. "Proposed testimony must be supported by appropriate validation *i.e.*, 'good grounds,' based on what is known. In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." *Id.*

myelopathy. Some people use denture cream and some people have a myelopathy; it is possible (and depending on the incidence of myelopathies, likely) that some denture-cream users have an idiopathic myelopathy simply due to the background distribution of that disease. Without a baseline, any incidence may be coincidence. Accordingly, the absence of this data is a substantial weakness in Plaintiffs' experts' causal reasoning.

d. Understanding of the Physiological Processes Involved

"When [mechanistic evidence] is present it can greatly strengthen a causal inference, but when it is absent it does not necessarily undermine the inference." CRANOR 247; *see also* Green, REFERENCE MANUAL 378 ("When biological plausibility exists, it lends credence to an inference of causality."). Although Plaintiffs' experts are able to explain at least one[25] of the biological processes by which zinc interferes with copper absorption,[26] they

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[25] Dr. Brewer:

> Q. Okay. Now, are there various postulated mechanisms by which zinc might affect copper status?
>
> A. Yes.

(Brewer Dep. 46:15–17).

[26] Zinc causes an upregulation of metallothionein production in the enterocytes. Copper has a higher binding affinity for metallothionein than zinc. Thus, copper displaces zinc from metallothionein, remains in the enterocytes and is then lost in the stool as intestinal cells are sloughed off. Thus, there is a clear biological mechanism for excessive zinc ingestion causing copper deficiency.

(Lautenbach Rep. ¶ 15).

acknowledge that "the mechanism by which hypocupremia leads to neurologic abnormalities in humans remains uncertain."[27] (Brewer Dep. 38:24–39:9). Moreover, there is no mechanistic evidence concerning the absorption of zinc from the Fixodent polymer, leaving its experimentally determined decreased bioavailablity unexplained. The Court acknowledges the mechanistic explanation of how zinc up-regulation of metallothenien leads to copper loss does lend some support the conclusion that Fixodent can block copper absorption. However, this supports only one premise in Plaintiffs' multi-step hypothesis; and the limited bio-availability of the zinc in Fixodent suggests this conclusion must be held tentatively.

e. Clinical Studies

The clinical trial, or randomized-trial, is a type of analytical epidemiological evidence, but this type of evidence is unlikely to be available in a toxic-tort case because it is unethical to randomly assign a human individual a potentially harmful dose of a suspected toxin. *See* Green, REFERENCE MANUAL 338 ("Ethical and practical constraints limit the use of such experimental methodologies to assessing the value of agents that are thought to be beneficial to human

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[27] Dr. Brewer:

> Q. Going back to the zinc-induced copper deficiency syndrome that you referred to in your report, do you know if it has been scientifically established what the mechanism is whereby a deficiency in copper supposedly causes a myelopathy?
>
> A. No, I don't believe that there's a scientifically established mechanism.

(Brewer Dep. 30:12–18; *see also* Greenberg Dep. 30:12–18).

beings.")). Courts do not demand and should not demand the results of a randomized, controlled study to prove causation in toxic-tort cases. Thus, the lack of a randomized, controlled experimental study showing that Fixodent causes copper-deficiency myelopathy does not undermine Plaintiffs' experts' inference of causation.[28] It should be noted that the record is not completely devoid of evidence from clinical trials: both Dr. Brewer's experiments to determine what dose of zinc acetate is necessary to place individuals into a negative copper balance and Procter & Gamble's pharmacokinetic studies are clinical-trial evidence. However, neither of these studies is dispositive of the ultimate question of whether Fixodent can cause copper-deficiency myelopathy.

While this ultimate question could not be subjected to a clinical study, it may be appropriate, practical, and ethical to conduct a clinical study to determine at what dose Fixodent may induce a negative copper balance. Such a study would bridge the gap between Dr. Brewer's copper-balance studies and Procter & Gamble's pharmacokinetic studies. It would not, however, allow one to infer the exposure to Fixodent required to induce the severe copper deficiency that Dr. Brewer testified would be necessary to produce neurological symptoms. (*See* Brewer Dep. 19:11–17 ("If I had to guess, I would say that you would have to have the copper down in the very low range for at least a few months before you develop the neurologic disease.")).

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[28] However, as discussed, the lack of *any* analytic epidemiological studies does weaken Plaintiffs' experts' assertion of causation.

2. Plaintiffs' Experts' Data and Methodologies

Plaintiffs and their experts rely on several bases to support their inference of general causation: (1) a biologically plausible explanation, (2) case reports of denture-cream users who have neurological problems, (3) de-challenge evidence, (4) animal studies, and (5) an FDA notice.

a. Biologically Plausible Explanation

As discussed, a biologically plausible hypothesis can lend credence to a causal inference. Plaintiffs' experts hypothesize a multi-step causal chain linking the ingestion of Fixodent to a myelopathy. The experts rely on different types of evidence to support each premise in their hypothesis and then infer, based on their scientific judgment, that Fixodent can cause copper-deficiency myelopathy. The question before the Court is whether this ultimate inference is reliable. Making some of the implicit premises explicit,[29] Plaintiffs' hypothesis can be summarized as follows:

(1) Fixodent contains zinc.

(2) The zinc in Fixodent can be absorbed by the body.

(3) Absorption of enough zinc from any source can induce a negative copper balance.

(4) One can ingest enough zinc from Fixodent to place the body in a negative copper balance.

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[29] There are others which remain implicit such as assumptions about the amount of dietary copper consumed by denture wearers.

(5) Over time a zinc-induced negative copper balance can lead to a copper deficiency.

(6) A prolonged copper deficiency in humans can cause a myelopathy.

(7) Therefore, Fixodent can cause a myelopathy.

There are several reasons this hypothesis is not a basis from which to infer causation. First, as discussed, Plaintiffs do not have any analytical epidemiological evidence showing that (4) is true; that is, that one can ingest enough Fixodent to induce a negative copper balance. Plaintiffs' experts also assume the truth of (5) without pointing to any analytical epidemiological evidence to show that it is true. Moreover, premise (6), that a copper deficiency can cause a myelopathy, is subject to ongoing scientific debate and is supported at present only by a few case reports.

Second, Plaintiffs' attorneys have treated this hypothesis like it is a deductive argument.[30] (*See* Brewer Opp'n 2 [ECF No. 1071] ("Defendants and their experts have chosen to ignore long-accepted,

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[30] [I]nferences to conclusions are of two kinds: deductive and non-deductive. The defining feature of valid deductive inferences . . . is that the conclusion is 'guaranteed' logically or semantically by the premises. . . . By contrast, nondeductive inferences are simply those whose conclusions are supported but not guaranteed by their premises. Even if the premises are true, the nondeductive link between premises and conclusions will have varying degrees of strength, unlike a deductive argument. In nondeductive arguments if the premises are true, they may offer much to little (or no) support for the conclusion in question. Moreover, the given premises will provide support for different possible conclusions . . . .

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axiomatic scientific principles of zinc metabolism."); *see also id.* at 12 ("The case reports are not required to establish a causal link between the ingestion of excessive zinc and disease. That link has been known and understood for decades."); Hr'g Tr. at 93:20 ("There's no missing link."). Although Plaintiffs' hypothesis resembles a deductive argument, it should not be confused for one. It is not the case that if, as Plaintiffs' attorneys claim, every premise is generally accepted by the scientific community, that the conclusion is accepted as well.

In reality, Plaintiffs' argument is a type of inductive argument where some premises have a statistical component:

(1) Fixodent contains zinc.

(2) Excessive zinc ingestion, including from Fixodent, increases the risk of copper deficiency.

(3) Prolonged copper deficiency increases risk of a myelopathy.

(4) Therefore, Fixodent increases risk of a myelopathy.

As this makes apparent, general agreement on the truth of the premises would not guarantee Plaintiffs' conclusion is true.[31]

Third, in forming this hypothesis and concluding it supports causation, there is no indication Plaintiffs'

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[31] Consequently, the Court need not address whether zinc intake can cause copper deficiency (probably, in some people), or whether copper deficiency can cause myelopathy (maybe, in some people) because it would be unreliable for Plaintiffs' experts to infer from those premises — even if true — that Fixodent causes copper-deficiency myelopathy.

experts or the authors of the articles tying denture cream to a myelopathy engaged in systematic scientific reasoning to conclude this hypothesis is the best explanation for what they observed in the case reports.[32] For instance, "in trying to understand causal relationships a researcher needs to consider a sufficiently complete list of plausible explanations to account for the evidence." CRANOR 130. Thus, before inferring Plaintiffs' hypothesis, that Fixodent causes a myelopathy is the best explanation for the neurological symptoms reported in the case reports, researchers should form a list of competing hypotheses. Those rival hypotheses should then be ranked "according to their plausibility based on the evidence available at the time." *Id.* at 131. Next, the researcher should "use the initial plausibility rankings to try to distinguish what other evidence might be available that would distinguish between the explanations — to separate more plausible from less plausible explanations — and seek it out." *Id.* Then all relevant evidence should be used to determine which hypothesis is the most likely. There is no evidence that Plaintiffs' experts or the case reports they rely on have been systematic in considering other plausible hypotheses[33] and

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[32] The flaws in the methodologies of the case report articles, particularly the Hedera and Nations Articles, are discussed in detail below.

[33] One interesting possibility is that denture wearers, particularly those using ill-fitting dentures, are more vulnerable to copper deficiency due to different eating habits caused by their dentures that lead to lower calorie intake and nutrient deficiencies. (Nelson Rep. 27–29 (citing NR Sahyoun *et al., The nutritional status of the older adult is associated with dentition status*, 103 J. AM. DIETET. ASSOC. 61-66. (2003) [hereinafter

excluding background risk. Plaintiffs' hypothesis, understood as a biological explanation, is not a reliable basis for their experts to conclude that Fixodent causes copper-deficiency myelopathy.[34]

b. Case Reports

Beyond their hypothesis itself, Plaintiffs' experts' conclusion that Fixodent can cause copper-deficiency myelopathy is almost entirely based on the information contained in a number of scientific

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Sahyoun 2003])). This might also raise interesting egg-shell plaintiff questions.

[34] Dr. Landolph acknowledged that a hypothesis should be tested before concluding it is correct:

> Q. Once the hypothesis is generated, then from a scientific standpoint the hypothesis should be tested, correct?
>
> A. Yes, it should be tested experimentally, yes.

(Landolph Dep. 28:11–21 [ECF No. 1144-1]).

Moreover, in verifying his hypothesis that zinc-acetate could control copper levels in Wilson's disease patients, Dr. Brewer "did a large number of copper balance studies and obtained results which confirmed [his] hypothesis." (Brewer Rep. 5 [ECF No. 1046-1]). This shows the level of intellectual rigor that has characterized Dr. Brewer's past work, but also highlights that he has not applied the same level of experimental rigor to confirm the link between Fixodent and copper-deficiency myelopathy. *See Kumho*, 526 U.S. at 152 ("The objective of [*Daubert's* gate-keeping requirement] . . . . is to make certain that an expert . . . employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field."); *see also Kilpatrick*, 613 F.3d at 1336 ("'Under the regime of *Daubert* . . . a district judge asked to admit scientific evidence must determine whether the evidence is genuinely scientific, as distinct from being unscientific speculation offered by a genuine scientist.'") (quoting *Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1316–17 (11th Cir. 1999)).

articles reporting cases of patients who used denture creams who also had abnormal levels of zinc and copper in their blood and neurological symptoms.[35] The Court has carefully reviewed this literature, as well as other scientific literature the experts mention in their reports.

"Causal attribution based on case studies must be regarded with caution." Green, REFERENCE MANUAL 475. Courts in the Eleventh Circuit have been particularly unwelcoming to experts who infer causation from case reports. *See*, *e.g.*, *Hendrix*, 609 F.3d at 1197 (finding case reports by themselves are "insufficient to show general causation"); *McClain*, 401 F.3d at 1254 ("[C]ase reports raise questions; they do not answer them."); *Rider*, 295 F.3d at 1199 (holding "case reports alone ordinarily cannot prove causation"); *Haggerty*, 950 F. Supp. at 1165 ("[W]hile case reports may provide anecdotal support, they are no substitute for a scientifically designed and conducted inquiry."). Nevertheless, the Eleventh Circuit has not foreclosed using case reports as supporting an inference of causation when

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[35] In addition to the Nations and Hedera Articles already cited, the other articles are: Hedera *et al., Myelopolyneuropathy and pancytopenia due to copper deficiency and high zinc levels of unknown origin*, 60 ARCH. NEUROL. 1303 (2003) ("Hedera 2003"); Spinazzi *et al., Myelooptico-neuropathy in copper deficiency occurring after partial gastrectomy*, 254 NEUROL. 1012 (2007); Sibley *et al., Myelodysplasia and copper deficiency induced by denture paste*, 84 AM. J. OF HEMATOL. 612 (2009); Afrin, *Fatal copper deficiency from excessive use of zinc-based denture adhesive*, 340(2) AM. J. OF THE MED. SCIS. 164 (2010); Spain *et al., When metals compete: a case of copper deficiency myeloneuropathy and anemia*, 5(2) NAT'L CLIN. PRAC. NEUROL. 106 (2009).

accompanied by other proof of causation.[36] *See McClain*, 401 F.3d at 1254.

In addition to it being unreliable, as a general matter, to rely on case reports to infer general causation, there are a number of particular problems with the case reports relied on by Plaintiffs' experts in this case. The report prepared by Procter & Gamble's expert, Dr. Lorene Nelson[37] (the "Nelson Report" [ECF No. 1046-12]), was extremely helpful to the Court in identifying the factual inaccuracies and methodological weaknesses[38] in the articles on which Plaintiffs' experts rely.

Dr. Nelson did an independent review of all of the literature concerning the link between zinc-containing denture cream and increased risk of a myelopathy. The total number of unduplicated cases

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[36] The only scientific literature supporting a link between copper deficiency and a myelopathy is contained in case reports and animal studies. A subset of those case reports links excessive zinc ingestion to copper-deficiency myelopathy. The Court focuses on this last set of case reports because those would provide the only direct support that Fixodent could cause a myelopathy. Recall from above, even if those intermediate premises were true, one could not reliably infer the conclusion that Fixodent causes myelopathy.

[37] Dr. Nelson studies the environmental causes of nervous system disorders and leads a large research program to identify environmental risk factors and susceptibility genes for neurodegenerative diseases. (*See* Nelson Rep. 4).

[38] Dr. Nelson observes that the case studies on which Plaintiffs' causation experts rely suffer from flaws such as incomplete data ascertainment, poor quality of exposure measurement, inconsistent case definition, and other sources of bias, and therefore provide even less support for the hypothesized causal association. (Nelson Rep. 9).

she found in the literature was 21. Within those 21 cases, ten patients reported using only Poligrip, four reported using both Poligrip and Fixodent, and one reported using Fixodent exclusively; the type of denture cream used in the remaining seven cases was not reported.[39] (*See* Nelson Rep. 12–13).

Dr. Nelson also observes that copper-deficiency myelopathy lacks widely accepted or published case definition criteria identifying its clinical features, imaging abnormalities, and clinical disease course. (*See id*. at 10). In Response, Plaintiffs argue there is a clear phenotype of patients who have zinc-induced copper-deficiency myelopathy and point to Dr. Greenberg's deposition testimony. (*See* Greenberg Dep. at 71:20-72:22 April 29, 2011 [ECF No. 1072-1]). However, Dr. Greenberg did not select the individuals in the case reports; the authors of those reports did, and what matters is what they thought the scope of the disease was. That is, the case reports may not have used Dr. Greenberg's definition of copper-deficiency myelopathy.

There are very good reasons to believe the cases reported in the literature suggesting an association

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[39] As discussed, the zinc in Fixodent is bio-available, but the pharmacokinetic studies show that its inclusion in the Fixodent polymer reduces its absorption as compared with more soluble forms of zinc. (*See* PK Study 35). Poligrip uses a different polymer, for which pharmacokinetic information is not available in this litigation, and contains twice the amount of zinc as Fixodent. These differences severely limit the conclusions that can be drawn from the cases where patients used Poligrip. Fixodent is not Poligrip, and neither is a tube of zinc. *See McClain*, 401 F.3d at 1246 ("'[E]ven minor deviations in chemical structure can radically change a particular substance's properties and propensities.'") (citation omitted).

between denture cream and neurological symptoms included people who were not suffering from copper-deficiency myelopathy. First, there is not a well-established clinical presentation for copper-deficiency myelopathy. Dr. Kumar, the author of some of the studies on which Plaintiffs' experts rely and who is cited by all of the case reports linking denture cream to a myelopathy, has written extensively on the clinical features of copper-deficiency myeloneuropathy. (*See* Nelson Rep. 10–11 (citing numerous articles by Kumar)). Dr. Kumar acknowledges that copper-deficiency myelopathy does not have a specific diagnosis code within the international classification of disease coding system. (*See id*. at 10 (citing Kumar *et al., Copper deficiency myeloneuropathy*, Medlink Neurology (Nov. 22, 2010), www.medlink.com (last visited June 13, 2011) [hereinafter Kumar 2010])). Second, in a recent article, Dr. Kumar specifically notes that some of the cases in the Nations Article would require additional study before they were classified as copper-deficiency myeloneuropathy. (*See id*. (citing Kumar 2010)). Moreover, a recent article surveying the literature on copper-deficiency myelopathy reached the same conclusion as Dr. Kumar and found that some of the conditions reported in the case reports may be "less clearly causally related to copper deficiency." (Nelson Rep. 10–11 (citing S.R. Jaiser *et al., Copper Deficiency Myelopathy*, J. NEUROL. 1 (Published Online 2010))).

Third, Dr. Boyer, one of the authors of the Nations Article, testified "the patients in our study had more of a neuropathy than a myelopathy, so involving the peripheral nerve rather than the spinal cord" (Boyer Dep. 32:10–14), which directly contradicts

Dr. Greenberg's description of Ms. Chapman's condition (*see* Greenberg Dep. 87:15–17 ("She doesn't have a peripheral neuropathy.")). These inconsistencies in case definition limit the evidentiary value of the case reports to support an inference of causation because it is not even clear all of the case subjects had copper-deficiency myelopathy.[40] *See* Green, REFERENCE MANUAL 379 ("A study that finds that an agent is associated with many different diseases should be examined skeptically.").

Dr. Nelson also notes that the Nations and Hedera Articles suffer from a number of methodological weaknesses that could introduce bias. First, it is not clear that the articles thoroughly excluded other sources of zinc to which the patients may have been exposed; neither the Nations or Hedera Article includes a description of the specific methods used to question patients about possible zinc exposure. In the absence of a standard set of questions for collecting exposure information it is likely that each patient underwent different questions administered in an open-ended format that may have biased the patients' responses.[41] Under those circumstances, it

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[40] As Dr. Nelson points out and the Court agrees, "there is considerable variability in the constellation of features that are presented for the patients that are presented for the subjects of the various anecdotal reports." (Nelson Rep. 11 (citing Nations and Hedera Articles)).

[41] Dr. Brewer:

> Q. . . . Was there a written questionnaire of any type that was to be utilized with regard to the patients that were contacted?

is possible that the patients were aware the studies were investigating the hypothesis that zinc-containing denture creams could be responsible for their condition.[42] This knowledge could have affected the subjects' answers during the interviews for the study.

There are also some specific reasons Plaintiffs' experts cannot rely on the Nations Report to support an inference of causation. The Nations Article phrases its conclusions tentatively, explaining:

> We speculate that the copper deficiency in these four patients was secondary to ingestion of denture cream . . . . These findings, while not

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> A. I assume you're referring to the questionnaire regarding dental adhesive, and not that I'm aware of. I think that after we became aware of the Nations article, then it was pretty obvious that you had to ask do you have ill-fitting dentures, do you use dental adhesives, and do you use — and what is its name and do you use a large amount of it, how much do you use. But those, that's an informal set of questions that the various investigators were asking these patients.
>
> Q. And the various investigators were free to ask those questions in any manner which they personally felt appropriate?
>
> A. Yes.

(Brewer Dep. 57:1–17).

[42] The case reports also do not consider the possibility of confounding bias. For instance, as discussed, at least one analytical study suggests that denture wearers, particularly those using ill-fitting dentures, have lower calorie intake and lower levels of several nutrients than dentate people. (Nelson Rep. 27–29 (citing Sahyoun 2003)).

> proving a causal relationship, warrant routine inquiry about the use of denture cream, in addition to zinc supplements, during the clinical evaluation of patients with myeloneuropathy and hematologic dysfunction.

(Nations Article 642). While it is common in scientific literature for investigators to couch their conclusions litotically, *see* CRANOR 192–197 ("Scientists tend to hedge their claims in scientific papers"), the conclusion of the Nations Article seems to the Court to be a sincere expression of uncertainty.[43] Because the authors of the Nations Article themselves do not conclude there is a causal relationship between the use of Fixodent and neurological symptoms, it is inappropriate for Plaintiffs' experts to draw that conclusion for them. *McClain*, 401 F.3d at 1248 (decrying "unauthorized conclusions from limited data — conclusions the authors of the study d[id] not make"); *In re Accutane Prods. Liab.*, No. 1626, 2009 WL 2496444, at *2 (M.D. Fla. Aug. 11, 2009) ("[W]hen an expert relies on the studies of others, he must not exceed the limitations the authors themselves place on the study."). Additionally, while the Nations Article states that all of the subjects' copper levels returned to normal after they stopped using denture cream, at least one patient continued to have depressed copper even with copper supplementation. (*See* Boyer Dep. 239:1–

[43] Indeed, Dr. Philip Boyer, who is one of the authors of the Nations Article, testified that a case-control or cohort study "would be a perfect thing to do. And as I mentioned, I proposed that to the dental faculty here as a study that would be good to do, but [it] has not been done." (Boyer Dep. 331:2-12).

240:15). Finally, none of the subjects in the Nations Article reported having used Fixodent.

The Hedera Article, which was co-authored by Dr. Brewer, also suffers from its own particular deficiencies.[44] First, there are methodological problems. In their deposition testimony, Drs. Hedera and Brewer acknowledged they did not establish a case definition or set of diagnostic criteria (*see* Brewer Dep. 34:7–24), they followed no written protocol (*see id*. 35:4–7, 56:6–25, 57:1–17), and they did not know how much denture cream the patients used (*see* Hedera Dep. 261:19–262:20, 263:4–9) or how long the patients had used denture cream (*see id*. 253:10–24). They also did not take the subjects' complete medical histories to exclude potential alternative causes for their neurological symptoms. (*See id*. 74:9–76:5, 79:2–80:6).[45]

Second, Dr. Brewer acknowledged in his deposition that there were inaccuracies in the Hedera Article. (Brewer Dep. 128:18–23 ("Q. So when the article says that their copper and zinc normalized after stopping denture cream, that's not an accurate statement, is it? A. It's got some inaccuracy to it . . . . It's somewhat inaccurate.)). Dr. Hedera also acknowledged that some patients in his article were inaccurately described as having abnormal blood zinc and copper levels when their lab results were

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[44] In her report, Dr. Nelson questioned whether the Hedera Article had undergone full peer review based on the rapidity with which the article moved from acceptance to publication. (*See* Nelson Rep. 17).

[45] The Hedera Article also estimates the bio-availability of the zinc in Fixodent. (*See* Hedera Article 2, 4). The pharmacokinetic studies suggest the estimate is much too high.

actually within the normal range. (*See* Hedera Dep. 277:8–14; 293:8–18; 297:7–10).

Some of these inaccuracies are very significant. The Article mischaracterizes the results to make it appear that all the patients' blood zinc and copper levels returned to the normal range[46] when the patients stopped using denture cream. (*See* Hedera Article Abstract). In fact, even after cessation of denture cream, seven of eight patients still had high urine zinc and six of eleven continued to have high plasma zinc. (*See* Brewer Dep. 127:25–129:14). In Dr. Brewer's expert report, in discussing the Hedera Article he states, "in this series of eleven patients the cessation of the use of the denture adhesives led to the normalization of zinc levels. In all eleven patients only the use of zinc containing denture adhesives could explain the clinical manifestations." (Brewer Rep. 8 [ECF No. 1046-1]). Dr. Brewer's conclusion is not reliable because it is based on an inaccurate factual premise.

Third, as mentioned, there is only one patient in all of the case reports who is described as having used Fixodent exclusively. That patient is documented in the Hedera Article as patient #2. (*See* Hedera Article 3). The case report does not identify how much Fixodent that patient used, but only states he, along with the other subjects, "reported applying large amounts of the denture creams." (*Id.* at 2). This

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[46] The subjects were given copper supplements when they were taken off denture cream. (*See* Hedera Article 2). Therefore, it is not clear whether it was the cessation of denture-cream use or copper supplementation that raised the subjects' blood copper levels. This particular confounding bias afflicts a number of the case-report articles.

single Fixodent user had near-normal zinc levels before stopping use of the product, and his copper level remained abnormally low after cessation; he also had "Axonal Polyneuropathy" rather than "Demyelinization." (*Id.* at 3). Case reports suggesting a link between denture cream and "axonal polyneuropathy" cannot act as reliable evidence of an association between Fixodent use and a *myelopathy*. *See McClain*, 401 F.3d at 1246 ("Evidence suggest[ing] that [a chemical] may cause ischemic stroke does not apply to situations involving hemorrhagic stroke. This is 'a leap of faith'. . . .") (quoting *Rider*, 295 F.3d at 1202).

The Court has also considered the other case report articles suggesting a link between zinc-containing denture cream and finds they suffer from their own methodological flaws. In particular, none specifies the subjects used Fixodent. Accordingly, an inference of causation based on this collection of case reports would be unreliable. *See* Ralph R Cook, *Epidemiology for Toxicologists* in PRINCIPLES AND METHODS OF TOXICOLOGY 559 (A. Wallace Hayes 5th ed., 2008) ("Although the theories derived from case studies are not always wrong, history teaches that they are seldom right.").

c. De-challenge Data

"When . . . eliminating exposure reduces the incidence of disease, this factor strongly supports causal relationship." Green, REFERENCE MANUAL 378. According to Plaintiffs, their experts cite the Nations and Hedera Articles "specifically to demonstrate that upon de-challenge with Fixodent, the patients in the studies saw their zinc levels normalize in short order and we[re] able to normalize

copper levels to the point where supplementation could be stopped in each." (Resp to Supp. Brewer Br. 19 [ECF No. 1167]). However, as a careful review of the Nations and Hedera Articles has just shown, only one of those patients exclusively used Fixodent, and many of the patients continued to have abnormal levels of zinc and copper in their blood and urine. Additionally, cessation of denture cream use was only sometimes followed by any neurological improvement by the patients in those articles. Accordingly, the de-challenge data does not reliably show that cessation of Fixodent leads to amelioration of the symptoms of copper-deficiency.

d. Animal Studies

Although some animal studies are mentioned in passing in Plaintiffs' experts' reports, no expert explicitly relies on them in forming his opinions. *See Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1314 (11th Cir. 1999) (citing *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 743 (3d Cir. 1994 ("[I]n order for animal studies to be admissible to prove causation in humans, there must be good grounds to extrapolate from animals to humans.")). Because Plaintiffs' experts do not even attempt to argue the animal studies can be extrapolated to humans, the Court will not make the argument for them. It will however, pause to note that swayback, a neurological disease caused in second-generation sheep whose mothers grazed in copper-deficient pastureland, provides little support for the claim that zinc-induced copper deficiency in humans leads to a myelopathy. *See* Bennetts, *et al., Copper Deficiency in Sheep in Western Australia: A Preliminary Account of the Aetiology of Enzootic Ataxia of Lambs and an*

Anaemia of Ewes, 13 AUST. VET. J. 138 (1937); *see also* Van Campen*, Zinc Interference with Copper Absorption in Rats*; 91 J. NUTR. 473 (1967) ([ECF No. 1072-6]). Moreover, at most these studies could supply support for some of the premises of Plaintiffs' hypothesis; as explained, one cannot infer causation from a hypothesis.

e. The Food and Drug Administration ("FDA") Notice

Dr. Lautenbach observes "[i]n response to the increasing adverse event reports, the FDA noted 'there are literature and research that suggest that zinc contained in some denture adhesives may be a contributing factor in these adverse events.'" (Lautenbach Rep. ¶ 40 (citing FDA Notice and Recommended Action — 2/23/11)). In his view the FDA's action shows the agency has acknowledged "a compelling signal for an association between Fixodent and myeloneuropathy." (*Id.* at ¶ 41). There are three problems with this argument. First, the FDA only recognizes an association, and "showing association is far removed from proving *causation*." *Allison*, 184 F.3d at 1315 n.16 (emphasis in original). Second, like in *McClain*, where the Eleventh Circuit found a more strident FDA warning not to be a sound basis for an inference of causation, the FDA Notice "relie[s] heavily on adverse event reports without sufficient controls." 401 F.3d at 1248. Third, regulatory agencies follow different standards than courts in toxic-tort cases. "The risk–utility analysis involves a much lower standard than that which is demanded by a court of law. A regulatory agency such as the FDA may choose to err on the side of caution. Courts, however, are required under the

Daubert trilogy to engage in an objective review of evidence to determine whether it has sufficient basis to be considered reliable." *McClain*, 401 F.3d at 1250. Accordingly, Plaintiffs' experts may not establish causation by reliance on the FDA Notice.

B. Specific Causation: Whether Dr. Greenberg Used a Reliable Scientific Methodology to Conclude Fixodent Caused Ms. Chapman's Illness.

Dr. Greenberg would testify that Ms. Chapman suffers from zinc-induced copper-deficiency myelopathy caused by her use of Fixodent. (*See* Greenberg Rep. 10–11 ("[A] diagnosis of copper deficiency myelopathy is certain . . . [and] in this patient, it was precisely the ingested zinc in the denture cream that caused her copper deficiency.")). To reach this conclusion, Dr. Greenberg performed a differential diagnosis.

A differential diagnosis or differential etiology "'is a standard scientific technique of identifying the cause of a medical problem by eliminating the likely causes until the most probable one is isolated.'" *Kilpatrick*, 613 F.3d at 1336 n.7 (quoting *Westberry v. Gislaved Gummi*, 178 F.3d 257, 262 (4th Cir. 1999)); *see also McClain*, 401 F.3d at 1252 (internal citation omitted) ("[A differential diagnosis is] the determination of which one of two or more diseases or conditions a patient is suffering from, by systematically comparing and contrasting their clinical findings."). In *Hendrix*, the Eleventh Circuit laid out the reliable procedure for conducting a differential diagnosis. The doctor must begin with a comprehensive list of potential causes, and then engage in "a medical process of elimination whereby

all possible causes of the condition are considered and ruled out one-by-one, leaving only one cause remaining." *Hendrix*, 609 F.3d at 1195.

To begin, although permitted in some circuits, the Eleventh Circuit does not allow general causation to be proved by a differential diagnosis. *Compare McClain*, 401 F.3d at 1253 ("In the absence of [a showing of general causation] . . . a differential diagnosis generally may not serve as a reliable basis for an expert opinion on causation in a toxic tort case."), *with Westberry*, 178 F.3d at 266 (4th Cir.) ("A reliable differential diagnosis provides a valid basis for an expert opinion on [general] causation."). This means "the district court must ensure that, for each possible cause the expert 'rules in' at the first stage of the analysis, the expert's opinion on general causation is 'derived from scientifically valid methodology.'" *Hendrix*, 609 F.3d at 1195 (quoting *Hollander v. Sandoz Pharm. Corp.*, 289 F.3d 1193, 1211 (10th Cir. 2002)). Recall that Dr. Greenberg's conclusion that denture cream can cause copper-deficiency myelopathy is based on the same case reports that Drs. Brewer, Landolph, and Lautenbach cite. (*See* Greenberg Rep. 1 ("Between 2007-2009, several publications established that zinc poisoning from certain denture adhesive creams are the most common cause of copper deficiency myelopathy.") (citing case reports including the Nations and Hedera Articles)).[47] Without a reliable basis to infer Fixodent causes copper-deficiency myelopathy, a differential diagnosis reaching that conclusion is, in

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[47] Dr. Greenberg also fails to consider that Fixodent is not 100 percent bio-available, as suggested by the pharmacokinetic studies. (*See* Greenberg Rep. 3).

effect, a detailed, unpublished case report. As discussed, case reports can support other evidence of general causation but are not reliable bases to infer general causation. Accordingly, Dr. Greenberg's differential diagnosis is not reliable as a matter of law in the Eleventh Circuit because he ruled-in and considered an etiology — Fixodent-induced copper-deficiency myelopathy — that has not been established to cause Ms. Chapman's disease.[48]

A second problem with Dr. Greenberg's differential diagnosis is that he did not rule-in all possible causes before he started ruling things out. The report itself contains a section titled "Consideration of alternative diagnoses" where Dr. Greenberg lists, in addition to copper-deficiency, three other potential causes of Ms. Chapman's neurological syndrome: structural spinal cord injury, multiple sclerosis, and vitamin B12 deficiency. (*See* Greenberg Rep. 2–3). For Ms. Chapman's hematological syndrome, Dr. Greenberg ruled in lymphoproliferative disorders. (*See id.*). He also considered malabsorption and gastric bypass surgery as potential causes for her copper-deficiency. (*See id.*).

Defendants contend this list is much too short and that Dr. Greenberg should have also considered a

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[48] Plaintiffs make much of the fact that some of Defendant's experts acknowledge that a copper-deficiency myelopathy should be part of the differential diagnosis of Ms. Chapman. The Court has not decided whether there is such a thing as copper-deficiency myelopathy, it only decides there is no reliable basis on which Plaintiffs' experts may conclude there is such a thing as Fixodent-induced copper-deficiency myelopathy. The existence of copper-deficiency myelopathy is only one premise of Plaintiffs' hypothesis.

"long list of hereditary and acquired diseases that could potentially cause Plaintiff Chapman's myelopathy" including "adrenomyeloneuropathy, complicated hereditary spastic paraplegia, . . . Charcot-Marie-Tooth disease . . . , hereditary motor and sensory neuropathy Type V, subtypes of spinocerebeller atrophy, . . . hereditary ataxia with neuropathy . . . . vitamin E deficiency, Sjogren's syndrome, sarcoidosis, HTLV-1, neuromylitis optica, and a multiple vitamin deficiency syndrome." (Brewer Mot. at 18 n.21). Defendants point out that "hereditary neuropathies, which include myelopathies, are far more common than copper-deficiency myelopathies," and thus Ms. Chapman's myelopathy is "more likely caused by a genetic condition than by Fixodent," especially considering her personal medical history. (Brewer Reply 9 [ECF No. 1089]).

According to Plaintiffs, Dr. Greenberg did consider all of these "and then moved on to consider the more likely alternatives until conclusively determining that Ms. Chapman suffered from [copper-deficiency myelopathy] and blood dyscrasias caused by zinc induced copper deficiency." (Brewer Opp'n 18). In his deposition, Dr. Greenberg testified:

> The differential diagnosis for a myelopathy of this particular nature, one that involves prominent dorsal column involvement, and also has this lower motor neuron degeneration, is extremely limited. It's copper deficiency and B12 deficiency. I really don't think other things are reasonable. One can always expand a differential diagnosis, *and we often do to be*

> *cautious and to not make mistakes*, but to have a reasonable differential, those are the ones.
>
> If one then throws in the hematological picture, an uncommon hematological picture that she's developed of anemia [and] neutropenia that baffled her doctors who saw her, including a hematologist, who stated that he did not feel this was due to B12 deficiency, then we're just left with copper deficiency.

(Greenberg Dep. 86:11–20).

Notably, Dr. Greenberg says "to be cautious and to not make mistakes," "[we often] expand a differential diagnosis" (*id.* 86:17–19), but acknowledges he did not do so here. This suggests that Dr. Greenberg did not employ "the same level of rigor that characterizes the practice of an expert in the relevant field" in reaching the diagnosis of Ms. Chapman. *Daubert*, 526 U.S. at 152. This is confirmed by Dr. Greenberg's decision to perform "a reasonable test" to address "the possibility of an . . . arterial venous malformation, in the thoracic spinal cord" after he wrote his report. (Greenberg Dep. 16:5–17:7). His failure to perform a test he considered reasonable before opining on the cause of Ms. Chapman's disease shows a lack of methodological rigor in reaching the diagnosis in his report. Dr. Greenberg also did not consider the possibility of an idiopathic cause for Ms. Chapman's myelopathy. *See Kilpatrick*, 613 F.3d at 1342 ("The failure to take into account the potential for idiopathically occurring [disease] — particularly when [the disease] is a relatively new phenomenon in need of further study — placed the reliability of [the Doctor's] conclusions in further doubt.").

For these reasons, Dr. Greenberg did not perform a reliable differential diagnosis in reaching the conclusion that Ms. Chapman suffers from zinc-induced copper-deficiency myelopathy. *Daubert* requires Dr. Greenberg's testimony on specific causation be excluded.

C. Testimony of Drs. Wogalter, Von Fraunhofer, and Raffa

Because the Court finds that no expert will be permitted to testify to general or specific causation, the testimony of Drs. Wogalter and Von Fraunhofer, who assume the toxicity of Fixodent as a predicate for their testimony, is likely no longer relevant. The same is true for Dr. Raffa's proposed testimony on Procter & Gamble's assets, which would be relevant to a punitive damages claim. Therefore, the Court will grant the Motions seeking to preclude these experts from testifying on relevancy grounds.

IV. CONCLUSION

Plaintiffs have put forth a superficially appealing hypothesis that prolonged use of very large amounts of Fixodent may cause copper-deficiency. Plaintiffs' experts have based their conclusions on a modest amount of animal studies, mechanistic processes, epidemiological studies, and case studies indicating elemental zinc in an unknown dose amount may cause a copper deficiency, which, if allowed to persist for an unknown time, may cause nervous system problems in some individuals. From this information, they induce that the zinc contained in the polymer in Fixodent can be absorbed in significant enough quantities to form the first link in the causal chain — the unknown dose of zinc.

This theory is not ridiculous, but neither is it necessarily true; it is ripe for testing. In short, taking everything together, there is enough data in the scientific literature to *hypothesize* causation, but not to *infer* it. Hypotheses are verified by testing, not by submitting them to lay juries for a vote. It may very well be that Fixodent in extremely large doses over many years can cause copper deficiency and neurological problems, but the methodology Plaintiffs' experts have used in reaching that conclusion will not reliably produce correct determinations of causation. In a toxic torts case, more reliable evidence is required. Accordingly, it is

ORDERED AND ADJUDGED as follows:

1. The Motion to Exclude the Opinions of Plaintiffs' Experts Drs. Brewer, Greenberg, and Landolph **[ECF No. 1040]** is **GRANTED**.
2. The remaining *Daubert* motions [**ECF Nos. 1041–1044**] are, of necessity, **GRANTED**.

DONE AND ORDERED in Chambers at Miami, Florida, this 13th day of June, 2011.

/s/ *Cecilia M. Altonaga*
CECILIA M. ALTONAGA
UNITED STATES DISTRICT JUDGE

cc: counsel of record