UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA
MIAMI DIVISION

Case No. 09-2051-MD-ALTONAGA

In re

DENTURE CREAM PRODUCTS LIABILITY LITIGATION.
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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 testimony of Drs. Brewer, Landolph, and Lautenbach concerns whether Fixodent is, in general,[2]

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

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])).

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 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

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[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 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).

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. (S*ee id.*). A 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.

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

II. LEGAL STANDARD

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

> 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 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

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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.")).

[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.

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.

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

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[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.

[10] Dr. Greenberg would testify, "[b]etween 2007–2009, several publications established that zinc poisoning from certain denture adhesive creams are the most common 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.")).

general causation. Those types of evidence and methodologies are drawn from toxicology and epidemiology and include the dose-response 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 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

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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).

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 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.

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[14] *See, e.g.*, DJ 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.

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 Dr. Brewer's Wilson's disease[17] research establishes some people

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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.

(*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

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* 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

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go into such details.")).

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

[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).

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 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 evidence consists of experimental and observational studies, while descriptive evidence consists of case studies and case

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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.

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 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

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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).

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

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[22] Dr. Brewer:

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

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

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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*.

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 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

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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).

[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).

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 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

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

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.")).

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.

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

(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.

(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, axiomatic scientific principles of zinc metabolism."); *see also id.* at 12 ("The case reports

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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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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' 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

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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.

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

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 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]

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[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 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

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 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

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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)).

[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).

supporting an inference of causation when 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 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

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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).

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 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

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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).

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

[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)).

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 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:

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[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?
> 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)).

> We speculate that the copper deficiency in these four patients was secondary to ingestion of denture cream . . . . These findings, while not 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. 239:1–240:15). 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,

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[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).

[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).

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 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

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[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.

[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.

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 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 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

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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).

[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.

"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 "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.

CECILIA M. ALTONAGA
UNITED STATES DISTRICT JUDGE

cc: counsel of record