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 All Cases

ORDER

THIS CAUSE came before the Court on Defendants, The Procter & Gamble Company, The Procter & Gamble Distributing LLC, and The Procter & Gamble Manufacturing Company's (collectively, "Defendants" or "Procter & Gamble['s]") Motion to Exclude the Opinions of Plaintiffs' General Causation Experts ("Motion") [ECF No. 2197], filed September 11, 2013. On October 15, 2013, Plaintiffs filed a Memorandum of Law in Support of Plaintiffs' Opposition to Defendants' Motion to Exclude . . . ("Opposition") [ECF No. 2218]. Defendants filed a Reply in Support of Defendants' Motion to Exclude . . . ("Reply") [ECF No. 2224], on November 1, 2013. The Court has carefully considered the extensive briefing by the parties; the thousands of pages of filings by the parties, including expert reports and depositions and scientific literature; oral arguments at a hearing [ECF No. 2333], held on November 19, 2013; and applicable law.

I. BACKGROUND

This is not the first time a *Daubert* motion seeking to exclude Plaintiffs' general causation experts has been decided by the undersigned in this multi-district litigation. Over three and a half years ago, in *Chapman, et al. v. Procter & Gamble Distributing LLC*, Case No. 9:09-CV-80625 (hereinafter, the *Chapman* case), the undersigned granted Procter & Gamble's motion to exclude the opinions of Plaintiffs' general causation experts. *See In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d 1345 (S.D. Fla. 2011) ("*Chapman Daubert* Order"); (*see also* June

13, 2011 Order [ECF No. 1194]). The *Chapman Daubert* Order summarized Plaintiffs' claims and evidence of general causation as follows:

> 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 tort case, more reliable evidence is required.

In re Denture Cream Prods. Liab. Litig., 795 F. Supp. 2d at 1367 (emphasis in original). Subsequent to the *Chapman Daubert* Order, the Court granted Procter & Gamble's Motion for Summary Judgment (*see* July 30, 2012 Order [ECF No. 1918]). On September 11, 2014, the Eleventh Circuit Court of Appeals affirmed the *Chapman Daubert* Order. *See Chapman v. Procter & Gamble Distrib., LLC*, 766 F.3d 1296, 1316–17 (11th Cir. 2014).

Since *Chapman*, Plaintiffs claim to have obtained new evidence in support of their argument that Fixodent can cause copper deficiency myeloneuropathy ("CDM"),[1] including clinical, epidemiological, background risk of disease, and dose-response relationship. According

[1] The parties and witnesses use a number of terms to refer to the constellation of neurological injuries allegedly caused by long-term use of Fixodent. Those terms include: myelopathy, a spinal cord disorder; neuropathy, a peripheral nerve disorder; myeloneuropathy, a disorder involving the spinal cord and the peripheral nerves; and copper deficiency myeloneuropathy, a type of myeloneuropathy caused by copper deficiency. (*See* Mot. 14 n.2; Opp'n 8 n.2). For ease of reference, and because it is the term most often used by the parties, the Court refers to the various neurological injuries alleged to result from Fixodent use as copper deficiency myeloneuropathy, or "CDM."

to Plaintiffs, the results of a recently-conducted Fixodent Blockade Study, along with new expert analysis from Dr. David W. Grainger ("Dr. Grainger"), a polymer chemist, regarding Procter & Gamble's *in vivo* pharmacokinetic studies and various *in vitro* studies, shows the zinc in Fixodent is bioavailable and chronic exposure to Fixodent can block copper uptake in the body. (*See* Opp'n 4).

Plaintiffs' epidemiology expert, Dr. Ebbing Lautenbach ("Dr. Lautenbach"), uses a new retrospective study, the "Gabreyes Study," as the basis for an "analytical epidemiological cohort study that proves a statistically significant association between denture adhesives with zinc and CDM." (*Id.* 3). According to Plaintiffs, Dr. Lautenbach's cohort study "identifies the background risk of CDM in the general population of people not exposed to denture cream with zinc versus the rate of CDM in the population who use denture cream with zinc." (*Id.* 3). Dr. Lautenbach's cohort study concludes the risk of CDM in the population exposed to zinc-containing denture cream is, at a minimum, eight times greater, and possibly as high as 54 times greater, than the risk faced by the general population. (*See id.* 3–4; January 10, 2013 Expert Report of Ebbing Lautenbach ("2013 Lautenbach Report") ¶¶ 26, 33 [ECF No. 2197-9]).

Regarding evidence of a dose-response relationship, Plaintiffs proffer testimony from Dr. Grainger; Dr. Martyn T. Smith ("Dr. Smith"), a toxicologist; and Dr. Frederick K. Askari ("Dr. Askari"), a pharmacologist, to identify "the amount and duration of Fixodent zinc exposure that will cause copper deficiency and resulting hematological and neurological injuries." (Opp'n 3).

In addition, Plaintiffs' experts continue to rely on case reports to develop their position on general causation. Plaintiffs identify several new case reports involving denture cream since *Chapman*. (*See id.* 102). Applying a Naranjo Adverse Drug Reaction Probability Scale ("Naranjo Scale") to the case reports and case series, Dr. Lautenbach concludes zinc-containing

denture adhesives are a "probable" cause of CDM. (*See id.* 100).[2]

Dr. Smith offers a conclusion using a "weight of the evidence" analysis. Based on his overall review of relative literature and studies, Dr. Smith concludes, "Fixodent denture cream use can cause excess zinc exposure leading to copper deficiency and subsequent toxic sequelae, including hematological (blood) injuries and myelopathy." (June 3, 2013 Expert Report of Martyn T. Smith ("June 2013 Smith Report") 8 [ECF Nos. 2197-13, 14]).

Dr. Joseph Prohaska ("Dr. Prohaska"), an expert in *Chapman*, provides an overview of the impact of copper status on the hematological system, in particular, hematological changes associated with copper deficiency and the impact of excess zinc on copper status and copper deficiency anemia. (*See* April 30, 2012 Expert Report of Joseph R. Prohaska ("Prohaska Report") 3 [ECF No. 2194-5]). Plaintiffs proffer Dr. Elizabeth M. Shuster ("Dr. Shuster"), a neurologist, for her testimony[3] that CDM is a generally accepted diagnosis, and excess zinc from zinc-containing denture creams such as Fixodent, can cause CDM. (*See* Opp'n 121).

Defendants' omnibus *Daubert* Motion challenges the reliability and significance of Plaintiffs' new general causation evidence and opinions — in particular the Fixodent Blockade Study and Dr. Lautenbach's cohort study — and argues the previously identified analytical gaps in Plaintiffs' chain of general causation from *Chapman* remain. In particular, Defendants contend Plaintiffs still cannot establish that: (1) someone can ingest enough zinc from Fixodent to place the body in a negative copper balance; (2) a prolonged negative copper balance from denture cream use can lead to a copper deficiency; (3) a dose-response relationship exists

[2] Dr. Steven A. Greenberg ("Dr. Greenberg") and Dr. Smith also rely on case reports in forming their expert opinions.

[3] Dr. Shuster did not issue an expert report. (*See* Supplemental Expert Disclosure and General Causation Rebuttal Disclosure for Dr. Elizabeth Shuster [ECF No. 2197-16]). She is also a specific causation expert.

between Fixodent and copper deficiency, much less myeloneuropathy; (4) Fixodent users face a greater risk of developing myeloneuropathy than the general population; or (5) a physiological mechanism explains how a copper deficiency can lead to a myeloneuropathy. (*See* Mot. 3).

In addition to challenging the general causation experts, Defendants challenge the proffered testimony of Plaintiffs' non-causation experts: Dr. Carl Cranor ("Dr. Cranor"), a professor of philosophy offered for his opinion on the "weight of the evidence" methodology; Dr. Michael S. Wogalter ("Dr. Wogalter"), a human factors/ergonomics and safety principles expert offered for his opinions about deficiencies in Fixodent's label; and Dr. Frederick A. Raffa ("Dr. Raffa"), a damages expert.

II. LEGAL STANDARD

Federal Rule of Evidence 702 "compels the district courts to perform the critical 'gatekeeping' function" concerning the admissibility of scientific and technical expert evidence. *United States v. Frazier*, 387 F.3d 1244, 1260 (11th Cir. 2004) (citing *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 589 n.7 (1993); *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 147 (1999)). Rule 702 provides:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if: (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue; (b) the testimony is based on sufficient facts or data; (c) the testimony is the product of reliable principles and methods; and (d) the expert has reliably applied the principles and methods to the facts of the case.

FED. R. EVID. 702. "The inquiry envisioned by Rule 702 is . . . a flexible one. Its overarching subject is the scientific validity — and thus the evidentiary relevance and reliability — of the principles that underlie a proposed submission." *Daubert*, 509 U.S. at 594–95 (alteration added; footnote call number omitted). Although the inquiry focuses "on principles and methodology,

not on the conclusions that they generate," *id.* at 595, "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. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997) (alterations added; citation omitted).

In deciding whether to admit expert testimony, the Eleventh Circuit requires district courts to assess 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 application of scientific, technical, or specialized expertise, to understand the evidence or to determine a fact in issue.

Frazier, 387 F.3d at 1260 (citing *City of Tuscaloosa v. Harcros Chems., Inc.*, 158 F.3d 548, 562 (11th Cir. 1998)). The proponent of the expert testimony bears the burden of establishing, by a preponderance of evidence, the expert's qualification, reliability, and helpfulness. *See Hendrix ex rel. G.P. v. Evenflo Co., Inc.*, 609 F.3d 1183, 1194 (11th Cir. 2010).

With regard to reliability — the primary point of dispute between the parties here — the Supreme Court suggests a non-exhaustive list of several factors to consider: 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. The court must undertake an independent analysis of each step in the logic leading to the expert's conclusions, as "any step that renders the analysis unreliable under the *Daubert* factors renders

the expert's testimony inadmissible." *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1245 (11th Cir. 2005) (internal quotation marks, citations, and emphasis in original omitted).

For cases involving alleged toxic substances, the Eleventh Circuit distinguishes between "cases in which the medical community generally recognizes the toxicity of the drug or chemical at issue," and "cases in which the medical community does *not* generally recognize the agent as both toxic and causing the injury plaintiff alleges." *Id.* at 1239 (emphasis added). The first category of cases includes "toxins like asbestos, which causes asbestosis and mesothelioma; silica, which causes silicosis; and cigarette smoke, which causes cancer." *Id.* For these cases, the focus is on plaintiff-specific questions of individual causation. *See id.* By contrast, in the second category of cases, the court is required to analyze individual causation and "undertake an extensive *Daubert* analysis on . . . the general question of whether the drug or chemical *can* cause the harm plaintiff alleges. This is called general causation." *Id.* (emphasis in original; alteration added; footnote call number omitted).

III. ANALYSIS

A. *McClain* Category One or Two

The Eleventh Circuit affirmed the finding in *Chapman* that the zinc in Fixodent is not a generally recognized toxin like asbestos or cigarette smoke, and thus it falls within the second *McClain* category. *See In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d at 1350; *Chapman*, 766 F.3d at 1304. As explained by the Eleventh Circuit, the medical textbooks and journals, as well as the expert testimony cited by Plaintiffs, "recognized an association between excess zinc and copper deficiency," but "fail[ed] to show that *the zinc compound in Fixodent* is in *McClain* category one of medically accepted, cause-and-effect toxins." *Chapman*, 766 F.3d at 1304 (alterations and emphasis added).

A review of the evidence presented by Plaintiffs in the current briefing demonstrates the Eleventh Circuit's holding and analysis from *Chapman* are still applicable. The "decades' worth of underlying scientific literature" Plaintiffs rely on to prove general acceptance — most of which was presented in *Chapman* — pertains to excess zinc and copper deficiency, or copper deficiency and neurological disorders; it is not specific to the zinc compound in Fixodent. (*See generally* Opp'n 16–20).

Of the 23 textbooks cited by Plaintiffs as evidence of general acceptance that zinc in Fixodent can cause CDM, only four even mention "denture cream," and none specifically mentions Fixodent. (*See id.* 10–12; Opp'n App. B [ECF No. 2217-1]). Moreover, of the four textbooks that contain a cursory reference to denture cream, only one[4] provides a citation to evidence supporting the claim that denture cream is associated with copper deficiency.[5] This textbook relies on the same case series — the Nations Article — the *Chapman Daubert* Order found suffered from a number of flaws and methodological weaknesses, did not report any subjects who used Fixodent, and was an inappropriate basis on which to infer causation.[6] *See In*

[4] (*See* Opp'n App. B, ROBERT B. DAROFF ET AL., BRADLEY'S NEUROLOGY OF INTERNAL MEDICINE 1996 (6th ed. 2012) (citing Nations, et al., *Denture Cream: An Unusual Source of Excess Zinc, Leading to Hypocupremia and Neurologic Disease*, NEUROL., 71:639–43 (June 2008) (the "Nations" article or series))).

[5] According to Plaintiffs, the lack of an underlying reference is evidence that a given disease is generally recognized in the medical community and that an exhaustive reference list is therefore unnecessary. (*See* Opp'n 15 (citing October 3, 2012 Deposition of Dr. Ebbing Lautenbach ("October 2012 Lautenbach Deposition Transcript") [ECF No. 2197-34]). The Court does not find support for this statement in the cited expert testimony. Further, Plaintiffs' expert explained the goal of a textbook is to "provide an overview of that disease entity," not to provide a "systematic review" of the underlying source literature." (Oct. 2012 Lautenbach Dep. Tr. 45:14–20).

[6] As evidence of general acceptance, Plaintiffs also cite the *Dietary Supplement Fact Sheet for Zinc*, published by the National Institutes of Health, Office of Dietary Supplements, which lists denture cream as a possible source of excess zinc. (*See* Opp'n 17). The fact sheet is also based on the Nations Article and is not considered persuasive evidence of the general acceptance of the toxicity of Fixodent. (*See* Opp'n, Ex. 3, 6 [ECF No. 2217-1]).

re Denture Cream Prods. Liab. Litig., 795 F. Supp. 2d at 1361–62; *see also Siharath v. Sandoz Pharm. Corp.*, 131 F. Supp. 2d 1347, 1370 (N.D. Ga. 2001) ("The statements in the treatises are clearly based on case reports and, therefore, provide no more support than the case reports themselves." (citation omitted)), *aff'd sub nom. Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194 (11th Cir. 2002); *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 990 (8th Cir. 2001) (affirming decision by district court not to rely on texts that were "largely grounded upon case reports and other anecdotal information").

Finally, Plaintiffs rely on a retrospective study as evidence of general acceptance that the zinc in Fixodent can cause CDM. (*See* Opp'n 9 (citing Alemayehu A. Gabreyes et al., *Hypocupremia Associated Cytopenia and Myelopathy: A National Retrospective Review*, 90 EUR. J. OF HAEMATOLOGY 1 (2012) ("Gabreyes Study") [ECF No. 2194-15])). The authors of the Gabreyes Study looked at "all cases of copper deficiency in Scotland over a 5-yr period using information from a national reference laboratory" and "assessed their haematological and neurological symptoms and signs, to further characterize the condition and identify signs that might prompt early treatment." (Gabreyes Study 1, 2). The authors found "copper deficiency is an under-recognized cause of several types of cytopenia," which, if left untreated, "can progress to significant neurological injury." (*Id.* 1).

Of the 16 subjects with copper deficiency analyzed in the Gabreyes Study, nine were reported to have used denture cream. (*See id.* 2). The authors note their review of cases of copper deficiency "highlights the association between long-term zinc exposure through dental fixatives and the subsequent haematological and neurological symptoms and signs described

elsewhere."[7] (*Id.* (footnote call number omitted)). As discussed in more detail below, there is no indication the denture cream used by the Gabreyes Study subjects was Fixodent, and showing an "association is far removed from proving *causation*." *Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1315 n.16 (11th Cir. 1999) (emphasis in original). Furthermore, the "elsewhere" the Gabreyes authors reference for "the association" are two articles, one of which relies on the Nations and Hedera[8] case series the *Chapman Daubert* Order found suffered from a number of flaws and methodological weaknesses;[9] the other contains no mention of denture adhesives.[10]

Particularly in light of the "[m]illions of consumers who have regularly used Fixodent for decades without complaint," *Chapman*, 766 F.3d at 1304 (alteration added; citation omitted), the Court concludes Plaintiffs have not demonstrated the medical community generally recognizes the zinc compound in Fixodent is on par with asbestos and cigarette smoke as *McClain* category one cause-and-effect toxins. Therefore, the Court undertakes its extensive *Daubert* analysis on the general question of whether Fixodent can cause CDM.

B. General Causation: Reliable Scientific Methodologies

The *Chapman Daubert* Order identified several types of evidence and methodologies determined by the Eleventh Circuit to be reliable bases for an inference of general causation — an understanding of the physiological mechanisms involved, clinical studies or tests, dose-response relationship, epidemiological studies, background risk of the disease — and determined

[7] Plaintiffs' expert uses the Gabreyes Study as the basis for developing a cohort study. The Court discusses both studies in more detail below.

[8] Hedera et al., *Myelopolyneuropathy and Pancytopenia Due to Copper Deficiency and High Zinc Levels of Unknown Origin II*, NEUROTOXICOLOGY (2009) (the "Hedera" article or series).

[9] *See In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d at 1361–63.

[10] (*See* June 27, 2013 Expert Report of Lorene Nelson ("2013 Nelson Report") 17 n.14 [ECF No. 2197-21]). Dr. Lorene Nelson ("Dr. Nelson") is Defendants' epidemiology expert.

Plaintiffs' experts failed to satisfy any of them. *See In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d at 1351–57. The Eleventh Circuit affirmed this conclusion, focusing on Plaintiffs' lack of epidemiological evidence, dose-response, or background risk of disease —methodologies the Eleventh Circuit "has recognized as indispensable to proving the effect of an ingested substance." *Chapman*, 766 F.3d at 1308. As noted by the Eleventh Circuit, "[b]ecause these experts have failed to demonstrate the primary methods for proving the zinc in Fixodent causes myelopathy, their secondary methodologies, including plausible explanations, generalized case reports, hypotheses, and animal studies are insufficient proof of general causation. This latter evidence could mislead the jury by causing it to consider testimony that was insufficient by recognized primary methodologies to prove using Fixodent causes myelopathy." *Id.* (alteration added).

Consistent with the *Chapman Daubert* Order and the Eleventh Circuit's affirmance, the Court will examine Plaintiffs' evidence in support of these reliable methods of proving general causation. If Plaintiffs fail to provide reliable evidence in support of the "primary methods" for proving Fixodent causes CDM — epidemiological, dose-response, background risk in particular — their secondary methods are considered insufficient. *See Chapman*, 766 F.3d at 1308.

1. The Physiological Processes Involved

Plaintiffs maintain at least one of the physiological processes by which zinc induces copper deficiency has been identified and is well-understood. (*See* Opp'n 4). As Dr. Lautenbach explains, "zinc causes an upregulation of metallothionein production in the enterocytes. Metallothionein is an intracellular ligand and copper has a higher affinity for metallothionein than zinc. Thus, copper displaces zinc from metallothionein, remains in the enterocytes and it is then lost in the stool as the intestinal cells are sloughed off." (April 30, 2012 Expert Report of

Ebbing Lautenbach ("April 2012 Lautenbach Report") 8–9 [ECF No. 2197-8]). While the "precise mechanism by which excess zinc intake resulting in copper deficiency leads to neurological injuries" remains unclear (June 2013 Smith Report 8), causation may still be established even when the causal mechanism is unknown. *See* Michael D. Green *et al.*, *Reference Guide on Epidemiology*, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 604 (Federal Judicial Center, 3d ed. 2011) ("When biological plausibility exists, it lends credence to an inference of causality.") (hereinafter Green, REFERENCE MANUAL 3d ed.)).

Plaintiffs rely on the Fixodent Blockade Study, Procter & Gamble and GlaxoSmithKline[11] *in vitro* studies, and Procter & Gamble pharmacokinetic *in vivo* studies, as evidence the zinc in Fixodent dissociates from Gantrez salt in Fixodent and becomes bioavailable. Once bioavailable, Plaintiffs argue, "[t]he effect of zinc to block copper absorption is not unique to zinc acetate or Galzin, but rather a class effect of multiple formulations of zinc." (June 3, 2013 Expert Report of Frederick K. Askari ("June 2013 Askari Report") 3 [ECF No. 2197-7]).

2. Clinical Studies

a) The Fixodent Blockade Study

Dr. Askari designed the Fixodent Blockade Study (*see* [ECF No. 2197-54]) to examine the short-term effects of Fixodent on copper absorption in the human body. (*See* Opp'n 67). The study was conducted in India and lasted 36 days, during which time 24 subjects were housed and fed a controlled diet. (*See* June 2013 Askari Report 12). Twelve subjects were randomly chosen and dosed three times daily with encapsulated Fixodent, for a daily total of 12 grams of

[11] GlaxoSmithKline is the manufacturer of SuperPoligrip, which contained zinc until 2010. (*See* April 30, 2012 Expert Report of David W. Grainger ("Grainger Report") 2 [ECF No. 2197-15]).

Fixodent containing approximately 204 milligrams of zinc.[12] (*See id.*). Six subjects were randomly chosen and dosed three times daily with encapsulated zinc acetate, for a daily total of 150 milligrams of zinc; and six subjects were randomly chosen and dosed three times daily with an encapsulated sugar placebo. (*See id.*). The study was blinded so neither the caregivers, scientists in the analytic lab, nor the study subjects knew which product was being taken by any individual subject. (*See id.*).

The subjects' feces, urine, and blood lab results were collected at various intervals. Over two time points at the beginning of the study (days 3, 4, and the morning of day 5), and at the end of the study (days 31, 32, and the morning of day 33), the subjects were dosed with a tracer dose of purified copper 65 to facilitate detection of the blockade of copper absorption. (*See id.* 12–13). The subjects' copper 65 levels were compared to the subjects' naturally occurring copper 63 levels. (*See id.* 13). Dr. Askari explains, "if copper is being blocked in the Fixodent and zinc acetate test subjects from exposure to the zinc in the test product (Fixodent) and positive control (zinc acetate), the ratio of their fecal output of copper 65 as compared to their fecal output of copper 63 would increase relative to the control subjects, who were not dosed with zinc. In short, a higher ratio of copper 65 to copper 63 reflects blocking of copper." (*Id.*).

Dr. Askari's report on the Fixodent Blockade Study contains two findings. First, Dr. Askari found the ratio of stool copper 65 to 63 at days 31-33 of the study was significantly different for the Fixodent and zinc acetate subjects as compared to the placebo subjects, and reflected a blockade of copper absorption in the subjects taking Fixodent and zinc acetate as compared to the placebo ("control") group. (*See id.*). Dr. Askari reported the difference in ratios of fecal copper 65 to 63 was statistically significant to a confidence interval of <0.1. (*See id.*).

[12] According to Dr. Askari, this amount is consistent with amounts used by consumers in case reports. (*See* June 2013 Askari Report 12).

Second, Dr. Askari found the subjects dosed with Fixodent and zinc acetate had a higher level of zinc in their urine as compared to the control subjects, which reached statistical significance <0.05. (*See id.*). According to Dr. Askari, this finding demonstrates the zinc in Fixodent is being orally absorbed and delivered to the urine similar to pharmaceutical dosing of zinc to lower copper for therapeutic reasons. (*See id.*). Dr. Askari opines the Fixodent Blockade Study, taken together and considered in the context of other evidence, shows Fixodent can cause CDM. (*See id.* 14).

Defendants challenge the reliability of the Fixodent Blockade Study in the face of "serious methodological flaws in the design, conduct and analysis" of the study (Mot. 18), as well as the overall relevance of the study's findings to the question of general causation, because the study "does not address the amount, frequency, or duration of Fixodent use needed to cause a copper deficiency, much less a myeloneuropathy" (*id.* 11). Plaintiffs dismiss Defendants' criticisms of the Fixodent Blockade Study's methodology, asserting flaws go to weight rather than admissibility. (*See* Opp'n 65, 76). In doing so, Plaintiffs ignore the Court's gatekeeping function under Rule 702, which requires the Court to focus on the scientific validity of the principles that underlie a proposed submission. *See Daubert*, 509 U.S. at 594–95.

Although Defendants and their experts contend there are numerous methodological flaws with the Fixodent Blockade Study, the Court focuses on those that impact the two findings Dr. Askari extracts from the study in support of Plaintiffs' theory on general causation. With regard to Dr. Askari's most significant conclusion — that the ratio of stool copper 65 to 63 is significantly different for the Fixodent subjects as compared to the control subjects, which reflects a blockade of copper absorption in the former group — there are several deviations

between the protocol approved by the Ethica Norma Ethical Committee[13] and the actual conduct and analysis of the Fixodent Blockade Study that call its reliability into question.

The protocol for the Fixodent Blockade Study identified the first primary endpoint to be "the mean increase in [copper 65] excretion in fecal matter above the baseline (mg/day) averaged over the study period . . . to test the hypothesis that the release of [zinc] either from Fixodent or Zinc Acetate impairs [copper 65] absorption as measured in feces." (Fixodent Blockade Study Protocol 8, Ex. B to August 30, 2012 Expert Report of Frederick K. Askari ("August 2012 Askari Report") [ECF No. 2197-4] (alterations added); *see also* June 27, 2013 Expert Report of Diane K. Jorkasky ("Jorkasky Report") 32 [ECF No. 2197-28]).[14] Instead of analyzing the change in fecal excretion of copper 65 over the study period, consistent with this pre-specified endpoint, Dr. Askari analyzed a ratio of copper 65 to copper 63 and limited the period of observation to days 31-33 of the study.[15] (*See* June 2013 Askari Report 13; Fixodent Blockade Study 12).

This particular change is notable in light of the testimony of Plaintiffs' statistician, Dr. Hongkun Wang ("Dr. Wang"), that after analyzing the fecal study data over the entire study period, no difference was detected between either the copper 65 or copper 63 output of the Fixodent group as compared to the control group. (*See* August 13, 2013 Deposition of Hongkun Wang ("Wang Deposition Transcript") 56:7–25 [ECF No. 2197-49]; *see also* Wang Analysis of

[13] The Ethica Norma Ethical Committee is an independent ethics committee that reviewed and approved Plaintiffs' application to conduct the Fixodent Blockade Study. (*See* Ethica Norma Ethical Committee approval letter, Ex. A to August 2012 Askari Rpt.; Fixodent Blockade Study 26).

[14] Dr. Diane K. Jorkasky ("Dr. Jorkasky") is an expert for Defendants, with experience in academic and industrial clinical research and clinical pharmacology. She submitted a report analyzing the Fixodent Blockade Study. The expert opinion of Dr. Jorkasky is not challenged in Plaintiffs' Omnibus *Daubert* Motion. ("Plaintiffs' *Daubert* Motion" [ECF No. 2201]).

[15] The comparison point was also changed from a "within-subject comparison" to a comparison between the Fixodent and placebo groups. (*See* Fixodent Blockade Study Protocol 9; Jorkasky Report 33).

Fixodent Blockade Study [ECF No. 2197-56] (noting "no clear treatment effect on Cu63 or Cu65"); *see also* June 20, 2013 Deposition of Frederick Askari ("2013 Askari Deposition Transcript") 69:21–24 [ECF Nos. 2197-31, 32, 33] (agreeing the total stool copper was not increased in the Fixodent group compared to the control group)). In contrast, when analyzing the ratio of stool copper 65 to 63, specifically at days 31-33 of the study, there is a statistically significant difference between the Fixodent and zinc acetate subjects as compared to the placebo subjects. (*See* June 2013 Askari Report 13).

The Court's concern with these changes in the statistical analysis — which make the data fit Plaintiffs' hypothesis — are not assuaged by Plaintiffs' assurances that it was the intention from the time of the design of the Fixodent Blockade Study to use a ratio of copper 65 to 63 as a primary endpoint, and this endpoint was simply articulated and clarified better in the final report. (*See* Opp'n 75–76). It is difficult to clarify something that was never articulated in the first place: the approved study protocol contains no mention of copper 63 in the primary endpoints, and the study sponsor, Dr. Salim Shah ("Dr. Shah"), could not identify a draft protocol that specified an analysis of a copper 65 to 63 ratio for feces. (*See* Fixodent Blockade Study Protocol 8; June 5, 2013 Deposition of Salim Shah ("Shah Deposition Transcript") 87:12–25; 476:2–536:12 [ECF Nos. 2197-46, 47, 48]). Also, it was not until *after* the study concluded that Dr. Shah asked Dr. Wang to analyze the data specifically for days 31-33 of the study. (*See* Fixodent Blockade Study 1 (noting study period ends on December 22, 2012); Shah Dep. Tr. 138:6–142:12 (instructing Dr. Wang, on March 8, 2013, to examine data from days 31-33)). Whether it was an intentional decision to change the pre-specified endpoint in light of unfavorable results from preliminary data analysis, or carelessness not to include in the study protocol the plan to examine the ratio of stool copper 65 to 63 during this limited time period, the Court finds either

reason is incompatible with reliable scientific methodology.

Another evident deviation from the study protocol pertains to the statistical endpoint. The difference in ratio of copper 65 to 63 between the Fixodent subjects and the control subjects was calculated as 0.057. (*See* Fixodent Blockade Study 12). The predetermined Type I error rate, or p-value,[16] for statistical significance was $p<0.05$. (*See* Fixodent Blockade Study Protocol 9 ("For pre-specified end points, a within-subject comparison will be made and statistical significance will be evaluated using student's paired test if $P<0.05$."); Jorkasky Report 33). In the final study report, however, this value was changed to $p<0.10$. (*See* June 2013 Askari Report 13 ("the difference in ratios of fecal Copper 65 to Copper 63 is statistically significant to a confidence interval of <0.1, which is quite impressive given the small number of subjects enrolled in the Study"); Fixodent Blockade Study 12).

Dr. Wang testified if the Type I error rate was 0.05, as initially set in the study protocol, the p-value of 0.057 would be "not significant" or "marginally significant," but at the changed p-value of 0.1 it is "definitely significant." (Wang Dep. Tr. 151:13–152:7). Moreover, Dr. Wang testified she chose the 0.1 p-value *after* she calculated the difference of 0.057. (*See id.* 153:15–18). Plaintiffs offer no explanation for the change in confidence interval levels, other than to admit 0.057 is not statistically significant to a confidence interval of 0.05, while claiming it is statistically significant at a confidence interval of 0.10. (*See* Opp'n 73).

Plaintiffs' willingness to change the pre-specified statistical endpoint — with the effect of turning a "not significant" study result into a "quite impressive" study result — again,

[16] Type I error rate, or p-value, defines the probability of rejecting the null hypothesis when in fact it is true. (*See* June 27, 2013 Expert Report of Robert D. Gibbons ("Gibbons Report") 4 [ECF No. 2197-27]). Dr. Robert D. Gibbons ("Dr. Gibbons") is a biostatistician for Defendants and submitted a report analyzing the Fixodent Blockade Study. Plaintiffs' *Daubert* Motion does not challenge Dr. Gibbons's opinions.

demonstrates a lack of objectivity and reliability. *See Perry v. United States*, 755 F.2d 888, 892 (11th Cir. 1985) ("A scientist who has a formed opinion as to the answer he is going to find before he even begins his research may be less objective than he needs to be in order to produce reliable scientific results."); *Rink v. Cheminova, Inc.*, 400 F.3d 1286, 1293 n.7 (11th Cir. 2005) ("In evaluating the reliability of an expert's method . . . a district court may properly consider whether the expert's methodology has been contrived to reach a particular result." (alteration added)).

In addition to reflecting a lack of objectivity, the foregoing deviations demonstrate the overall inadequacy of the Fixodent Blockade Study's predefined statistical analysis plan, and a statistical analysis plan that was developed after-the-fact. Each, on its own, is a departure from sound scientific practice.[17] Plaintiffs' Dr. Wang testified as a peer-reviewer she would have a study investigator fix a protocol that did not have an appropriate statistical analysis plan, and she would "definitely" be concerned if she knew the investigators did not follow the protocol's statistical plan and instead followed a statistical plan developed after the fact. (Wang Dep. Tr. 85:20–25; 87:18–25). The Fixodent Blockade Study's inadequate and fluid statistical analysis plan, taken together with the significant deviations from the study protocol, lead the Court to conclude Dr. Askari's first finding — that the difference in ratios of fecal copper 65 to 63 is

[17] According to Dr. Gibbons:

> The predefined statistical analysis plan contained within the [Fixodent Blockade Study] protocol was both inappropriate for the data collected in the actual study, and had nothing to do with the actual design of the study. In essence, there was no pre-defined statistical analysis plan for the study endpoints. . . . The statistical analysis plan included in the final clinical report was created after the study was unblinded, and was thus informed by the data (i.e., introduction of the ratio as the primary endpoint), leading to the potential for biased results. This is unacceptable research practice.

(Gibbons Report 5 (alterations added)).

statistically significant for the Fixodent and zinc acetate subjects as compared to the placebo subjects — is not based on sufficiently reliable and objective scientific methodology and cannot serve as the basis for Plaintiffs' general causation opinions.

In addition, other evidence in the record casts considerable doubt on the reliability of the remaining Fixodent Blockade study results. Two days before the study started, the Managing Director of Quest Life Sciences emailed study sponsor, Dr. Shah, explaining, "Blinding cannot be properly done as the capsule sizes are different," and "capsule size is so big that the compliance of subjects may be poor in taking the medication." (Nov. 14, 2012 Email [ECF No. 2197-59]). Based on Dr. Shah's response — "There is nothing written on the capsules and at least placebo and test product are of the same size, which is enough for blinding" (*id.*) — there is considerable concern the integrity of the blinding procedure was not maintained. In her report, Dr. Jorkasky highlights the importance of *all* of the administered capsules being *identical* — not just two of the three administered products being "of the same size."[18] (*See* Jorkasky Report 24).

There is also evidence indicating the samples obtained from the study may have been contaminated. An email from Dr. Shah to the Managing Director of Quest Life Sciences during the study notes "difficulties in storing samples at appropriate temperature" and feces samples "exposed to unfrozen and undesirable temperature conditions." (Nov. 27, 2012 Email [ECF No. 2197-62]). Dr. Shah writes, "I hope all other samples are appropriately collected and stored," and advises the manager to record all variances and provide an explanation of subsequent remedial steps taken to correct the variances. (*Id.*). It is unclear if Dr. Shah's advice was heeded. There appears to be no mention of the above incident in the Fixodent Blockade Study

[18] Dr. Jorkasky also observes there is "no record of the type, size and appearance of the capsule used in the preparation of Fixodent, the placebo, or zinc acetate;" "no documentation of the chemical composition of the placebo;" and no documentation to evidence which quality control guidelines were used to prepare the Fixodent capsules. (Jorkasky Report 24–25).

report. (*See generally* Fixodent Blockade Study).

The Court cannot turn a blind eye to the myriad, serious methodological flaws in the Fixodent Blockade Study and conclude they go to weight rather than admissibility. While some of these flaws, on their own, may not be serious enough to justify exclusion of the Fixodent Blockade Study; taken together, the Court finds Fixodent Blockade Study is not "good science," and is not admissible. *Daubert*, 509 U.S. at 593 (internal quotation marks and citation omitted).

b) *In Vitro* Studies: Dr. Grainger

Plaintiffs proffer the opinion of Dr. Grainger, a polymer chemist, as evidence of the "initial steps of the causal chain," and to allow Plaintiffs to argue "zinc is zinc regardless of the form in which it is ingested in the body and it impacts the body in the same manner (copper blockage) regardless of the initial source." (Opp'n 120). Based on Dr. Grainger's opinion, Plaintiffs claim when the zinc dose is adjusted, the impact of SuperPoligrip — which contains nearly twice the amount of zinc as Fixodent[19] — and Fixodent is the same. (*See id.* 117–118 ("Thus, a Fixodent user who used twice the amount of Fixodent as a SuperPoligrip user would have an equal amount of zinc in his or her body.")). Ultimately, Plaintiffs rely on Dr. Grainger's opinion to support their argument that case reports involving zinc-containing denture creams regardless of the brand, as well as case reports involving zinc supplements, "are all equally instructive" and should be considered in the general causation analysis. (*Id.* 117).

Dr. Grainger's report contains his findings regarding *in vitro* dissociation studies performed by Procter & Gamble and GlaxoSmithKline ("GSK") (*see* Grainger Report 2–3, 8), and his opinion regarding Procter & Gamble's *in vivo* pharmacokinetic/pharmadynamics

[19] Fixodent contains approximately 17 milligrams of zinc per gram of denture adhesive, whereas SuperPoligrip contains nearly twice that amount, 34 milligrams of zinc per gram. (*See* June 2013 Smith Report 53).

("PK/PD") studies, which he criticizes underestimate zinc ion release (*see id.* 3–8). Ultimately, Dr. Grainger reaches the following three conclusions: (1) Exposing zinc-containing Fixodent and SuperPoligrip denture adhesives to stomach pH will result in virtually complete dissociation of ionic zinc from the adhesives; (2) once dissociated, the zinc ions will be available to operate in their known mode of action — blocking copper in the duodenum and intestinal tract; and (3) "The chemical compositions of both Fixodent and [SuperPoligrip] are such that they will behave in a similar fashion with regard to zinc dissociation, muco-adhesion, and oral bioavailability . . . ."[20] (*Id.* 8–9).

According to Defendants, Dr. Grainger's opinions are irrelevant because he offers no conclusions on copper, the relationship between zinc and copper, the amount of zinc that will ultimately become available in the human body once Fixodent is ingested, how the human body will absorb or discard that zinc, and any longer-term effects from the ingestion of the zinc. (*See* Mot. 80–81). Defendants also argue Dr. Grainger's opinions are unreliable because Dr. Grainger does not offer any explanation of how zinc dissociation properties observed in *in vitro* release designs would transfer to a live human, and did not consider factors that might allow him to make such an extrapolation. (*See id.* 82–83).

Although the Court does not find Dr. Grainger's opinions to be irrelevant, it does find them unreliable. The *in vitro* dissociation studies are the foundation for all of Dr. Grainger's conclusions. The portion of his report dedicated to these studies, however, is barely one page and is completely devoid of any pertinent details or analysis. (*See generally* Grainger Report 2–

[20] "Dissociation refers to the separation of a polymer into various components under certain conditions. Bioavailability is different from dissociation and refers to the 'rate and extent to which a chemical or chemical breakdown product enters the general circulation, thereby permitting access to the site of toxic action.'" (Mot. 81 n.124 (quoting Joseph V. Rodricks, *Reference Guide on Exposure Science*, in REFERENCE MANUAL 3d ed. 545)).

3). His comments regarding "various *in vitro* release designs" and "some P&G studies," lack any citations to the referenced *in vitro* studies, any discussion about the study designs or methodology, and any details about the individual study results. (*See id.*); *see Ballard v. Keen Transp., Inc.*, No. 4:10-cv-54, 2011 WL 474814, at *4 (S.D. Ga. Feb. 3, 2011) (expert's failure to cite any specific chapter, page, or line on which he based his conclusions "makes it appear that he is not being as careful in his litigation consulting as he is in his ordinary professional work." (citing *Kumho Tire*, 526 U.S. at 152)). Based on his report, it is not even clear how many studies Dr. Grainger reviewed and whether he blindly accepted their results. *See In re TMI Litig.*, 193 F.3d 613, 715–16 (3d Cir. 1999) (finding expert's "failure to assess the validity of the opinions of the experts he relied upon together with his unblinking reliance on those experts' opinions, demonstrates that the methodology he used to formulate his opinion was flawed under *Daubert* as it was not calculated to produce reliable results.").

In the place of details and analysis, Dr. Grainger's one page *in vitro* report consists of conclusory statements, such as "Regardless of the experimental methodology used, however, in terms of percentage of zinc dissociated, the formulations behave similarly;" and "P&G and GSK study data make clear that there is near total zinc ion release from the adhesive products as formulated at stomach pH." (Grainger Report 2–3). "Presenting a summary of a proffered expert's testimony in the form of conclusory statements devoid of factual or analytical support is simply not enough. The party offering the expert must present the witness' proposed testimony in a form that persuades the trial court that the testimony will in fact assist the trier of fact. . . . [C]arrying this burden requires more than the *ipse dixit* of the expert." *Cook ex. rel. Estate of Tessier v. Sheriff of Monroe County, Fla.*, 402 F.3d 1092, 1113 (11th Cir. 2005) (alterations added; internal quotation marks and citations omitted)).

Moreover, Dr. Grainger's cursory comparison of Fixodent and SuperPoligrip — "Both Fixodent and [SuperPoligrip] contain Gantrez zinc salts and their formulations are similar to one another" (Grainger Report 2) — fails to recognize that "even small differences in chemical structure can sometimes make very large differences in the type of toxic response that is produced." David Eaton, *Scientific Judgment and Toxic Torts: A Primer in Toxicology for Judges and Lawyers*, 12 J.L. & POL'Y 1, 10–11 (2003) (hereinafter "Eaton"); *see also Rider*, 295 F.3d at 1201 ("Even minor deviations in chemical structure can radically change a particular substance's properties and propensities." (internal quotation marks and citation omitted)); *Evans v. Matrixx Initiatives, Inc.*, No. 3:07-cv-357-J-34JRK, 2009 WL 2914252, *7 (M.D. Fla. Feb. 18, 2009) (noting plaintiffs' reliance on zinc sulfate studies lacked sufficient reliability absent a demonstration that differences in chemical structure between zinc gluconate and zinc sulfate do not impact toxic effect).

In addition, as Defendants note, Dr. Grainger's report contains no explanation of how zinc dissociation properties observed in test tubes transfer to a live human, and Dr. Grainger did not consider factors allowing him to make a reliable extrapolation. He did not consider the amount of Fixodent ingested or the conditions under which it was ingested, the body's homeostasis processes and zinc excretion, or whether different zinc compounds would be absorbed at different rates. (*See* January 24, 2012 Deposition of David Grainger ("Grainger Deposition Transcript") 57:22–58:9; 65:20–66:1; 67:22–68:10 [ECF No. 2197-42]). Neither, apparently, did Dr. Grainger consider or compare how the *in vitro* studies using simulated gastric fluid, on which his opinions rely, relate to the *in vitro* studies using simulated intestinal fluid — which reflects the relevant site of action in this case — showing less than seven percent of the zinc in Fixodent dissociating. (*See* Reply 55).

Dr. Grainger's failure to explain the relevancy of the *in vitro* studies to humans or to account for factors needed to make a proper extrapolation is notable given his critique of Procter & Gamble's *in vivo* PK Studies, which, Dr. Grainger asserts, "did not accurately reflect users' chronic use and ingestion of orally pre-conditioned Fixodent, the amounts used, frequencies used, or gut processing and significantly different intrinsic metabolic variances in consumers." (Grainger Report 4). Indeed, Dr. Grainger's harshest critique of Procter & Gamble is Procter & Gamble's attempt to draw conclusions about how zinc ions are released in humans based on *in vitro* studies. In his report, Dr. Grainger states, "Attempted justification by [Procter & Gamble] . . . that negligible quantities of zinc ions are released *in vivo* because they observed no ion release in pure water at 25 degrees from an unstirred dialysis bag *in vitro* is a *completely scientifically and physiologically unjustified and unfair comparison*." (*Id.* 3 (emphasis added)).

In light of the noted severe inadequacies of his report and his failure to consider how the near complete release of all zinc ions in an *in vitro* study correlates to actual zinc ion release in the human body, Dr. Grainger's conclusions — which are all based on the *in vitro* studies — are unreliable.[21] *See Kilpatrick v. Breg, Inc.*, 613 F.3d 1329, 1340–41 (11th Cir. 2010) (affirming finding *in vitro* study did not support expert's opinion of a direct causal link where the authors of the study "could not state how their test results would transfer when conducted on a live human subject"); *Ballard*, 2011 WL 474814, at *3 (noting "the reliability of an *in vitro* experiment depends on whether it is predictive of *in vivo* experiment outcomes" (citation omitted)); *In re*

[21] Even if Dr. Grainger's opinions are reliable, the Court notes a speculative leap between his opinions regarding dissociation and bioavailability and Plaintiffs' argument that all case reports involving denture creams and zinc supplements are equally instructive. Dismissing the fact that SuperPoligrip contains nearly double the amount of zinc than Fixodent — which Dr. Grainger mentions once and the significance of which he does not analyze (*see* Grainger Report 9) — ignores the "'hallmark of basic toxicology'" that is the dose-response relationship. *McClain*, 401 F.3d at 1242 (quoting Eaton 15).

Accutane Prods. Liab., 511 F. Supp. 2d. 1288, 1294–95 (M.D. Fla. June 15, 2007) ("'The problem with this approach is also extrapolation — whether one can generalize the findings from the artificial setting of tissues in laboratories to whole human beings.' That is, studies such as these necessarily remove the cells from the dynamic metabolic context in which the human body actually processes chemical compounds." (quoting Michael D. Green *et al.*, *Reference Guide on Epidemiology*, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 333, 346 (Federal Judicial Center, 2d. ed. 2000))).

c) The PK Studies

In 2009 and 2010, Procter & Gamble conducted a series of pharmacokinetic studies (hereinafter "PK Study 1" and "PK Study 2"; collectively, the "PK Studies"), "to better understand the oral bioavailability of zinc in Fixodent compared to a well studied and highly bioavailable zinc salt, Galzin ® (zinc acetate)." (July 29, 2012 Expert Report of David A. Johnson ("Johnson Report") 3 [ECF No. 2197-22]).[22] The first study, PK Study 1, was conducted in two phases. In the first phase, 12 male subjects received either 50 milligrams zinc acetate capsules or capsules containing three grams of Fixodent (approximately 50 milligrams of zinc), with six subjects in each group. (*See id.* 3). In the second phase, 12 male subjects participated in a crossover design study in which all subjects received either 50 milligrams of zinc acetate or six grams of Fixodent (approximately 100 milligrams of zinc), and after a "washout period," were dosed with the other formulation. (*See id.* 3–4). The second study, PK Study 2, involved 20 subjects, 12 males and eight females, who were administered either 25 milligrams zinc acetate or six grams of Fixodent (approximately 100 milligrams of zinc). (*See*

[22] Plaintiffs' *Daubert* Motion challenges Dr. Johnson's opinion regarding the reliability of case reports, patient histories, and patient memories as being outside his expertise as a toxicologist. (*See* Plaintiffs' *Daubert* Mot. 41). Plaintiffs do not challenge Dr. Johnson's opinions pertaining to the PK Studies.

id. 4). The subjects were admitted in the evening, fasted overnight, were given either zinc acetate or Fixodent, had their blood drawn after eight hours, and were then released. (*See* June 2013 Smith Report 59).

According to Defendants' toxicology expert, Dr. Johnson, the PK Studies demonstrate the zinc in Fixodent is not 100 percent bioavailable, but has only limited bioavailablity on the order of 10 percent as compared to the highly absorbable zinc acetate. (*See* Johnson Report 17). Dr. Johnson explains the PK Study 2 "demonstrates that the absorption of zinc from 6g Fixodent (100mg zinc) is less than half of what is absorbed from 25mg zinc acetate," and "Fixodent users who overuse the product have a decreased ability for absorbing zinc compared to those who use Galzin." (*Id.*).

The PK Studies are not new evidence. In *Chapman*, the undersigned found the PK Studies were not dispositive of the ultimate question of whether Fixodent can cause CDM. *See In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d at 1357. Because the PK Studies suggested Fixodent was less bioavailable than zinc acetate, one could not reliably infer how much Fixodent was necessary to consistently induce a negative copper balance based on the large body of Wilson Disease research showing some people are placed into a negative copper balance with a single 25 milligram dose of zinc acetate.[23] *See id.* at 1353. The undersigned further found "there is a large analytical gap between the proposition that a 25mg 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 25mg of zinc per day for many years will develop a severe copper deficiency with neurological symptoms." *Id.*

[23] "In Wilson Disease, the lowest dose that has been tested is a single 25mg dose of zinc acetate per day. . . . [T]his amount was sufficient to place some Wilson Disease study subjects into a negative copper balance within just 30 days." (June 2013 Askari Report 8 (alterations added)).

In the present round of briefing, Defendants argue the PK Studies cannot be used to reliably infer a causal relationship because the studies do not address the amount, frequency, or duration of Fixodent use needed to cause myeloneuropathy or copper deficiency. (*See* Mot. 39). In addition, Defendants maintain the results of the PK Studies are not helpful to Plaintiffs' general causation theory because the studies found no changes in the subjects' blood copper levels or ceruloplasmin[24] levels after Fixodent ingestion, and they tend to indicate that taking more and more Fixodent may not expose someone to more and more zinc. (*See id.*).

The parties agree serum zinc levels are not an indication of zinc's ability to inhibit copper absorption in the relevant site of action, the intestines.[25] As Plaintiffs' biochemistry expert, Dr. Prohaska notes, "higher than normal zinc in the [gastrointestinal] tract has been shown to impair copper absorption, *not* urinary zinc or *plasma zinc levels*. While plasma and urinary zinc levels may correlate with dietary or [gastrointestinal] exposure[,] it is important to focus upon exposure to zinc at the site of action, the gut, *not blood* or urine concentrations." (Prohaska Report 8–9 (alterations and emphasis added)). Without the Fixodent Blockade Study — which attempted to focus on the exposure to zinc at the site of action — the PK Studies are the only potential evidence of the bioavailability of the zinc in Fixodent. Demonstrating the zinc in Fixodent is as bioavailable as Galzin, or zinc acetate, is a crucial link to proving the relevancy of Wilson Disease research, sickle cell anemia research, and copper balance studies.

[24] Ceruloplasmin is a copper-binding protein. (*See* July 26, 2012 Expert Report of Timothy R. Koch ("2012 Koch Report") 8 [ECF Nos. 2197-24, 25]).

[25] One of Dr. Askari's own conclusions is that the PK Studies "were fundamentally flawed because they did not test the known site of action or test copper blockage, like the Fixodent Copper Blockade study did." (June 2013 Askari Report 25). According to Defendants, "the PK Studies measured short-term zinc levels in the *blood* after subjects ingested capsules of Fixodent on *empty* stomachs. But increased zinc levels in the *blood* cannot reliably determine whether zinc is inhibiting copper absorption in the *intestines*."[25] (*Chapman*, Procter & Gamble Brief of Appellees 49 [ECF No. 2125-3] (emphasis in original)).

Despite this limitation on the relevance of the serum zinc measurements from the PK Studies, Plaintiffs' experts claim the studies provide evidence of the bioavailability of the zinc in Fixodent and support for a dose-response relationship between Fixodent and CDM. (*See* Opp'n 79). Relying on the uncorrected serum zinc values, Plaintiffs' toxicology expert, Dr. Smith, asserts the results of the PK Studies show that for both three-gram and six-gram doses of Fixodent, the zinc plasma levels rose in all subjects, thus showing Fixodent is bioavailable. (*See* June 2013 Smith Report 60). Dr. Smith then compares the uncorrected serum zinc values representing the total dose of zinc entering the bloodstream — calculated as the "Area Under the Curve" (or "AUC") — between the Fixodent and zinc acetate subjects, and concludes the values show 80 percent of zinc in Fixodent is bioavailable in humans. (*See id.* 60–63).

Notwithstanding these observations and calculations, Dr. Smith concedes PK Study 1 found no change in copper levels or ceruloplasmin levels, and "the zinc in Fixodent may not be as fully bioavailable as the Galzin in zinc acetate." (September 25, 2012 Deposition of Martyn T. Smith ("September 2012 Smith Deposition Transcript") 94:17–95:9; 97:13–16 [ECF No. 2197-40]). Furthermore, he concludes, PK Study 1 shows "the AUC are essentially the same in the uncorrected data for both 3g and 6g of Fixodent, showing that on average *the additional zinc in 6g dose [of Fixodent] is not absorbed over and above that in the 3g dose*." (June 2013 Smith Report 61 (emphasis and alteration added); *see also* Sept. 2012 Smith Dep. Tr. 95:14–25). Thus, while the parties might dispute the reason behind this finding,[26] all are in agreement that taking

[26] The parties' experts disagree on the reason for this finding. Dr. Smith opines it "is more likely than not due to the fact that zinc absorption is typically saturated after a 50 mg dose." (June 2013 Smith Report 61). Defendants' expert, Dr. Johnson, relying on corroborative data from PK Study 2 showing the absorption of zinc from six grams Fixodent (100 milligrams zinc) is less than half of what is absorbed from 25-milligram zinc acetate, opines the explanation lies in the lower bioavailability of zinc in the Fixodent Gantrez polymer. (*See* Johnson Report 17). Dr. Smith discounts the results of PK Study 2, explaining, "The results of PK1 show this was an unfair comparison biased in favor of the Fixodent product because zinc absorption became saturated at 50mg in PK 1 and so the use of a 100mg dose in

more and more Fixodent does not necessarily expose a person to more and more zinc.

Plaintiffs' pharmacology expert, Dr. Askari, does not make any specific calculations regarding the bioavailability of the zinc in Fixodent. Relying primarily on the uncorrected serum zinc values from the PK Studies, Dr. Askari makes several observations, including: (1) with single three-gram and six-gram doses of Fixodent, biologically available zinc was released from the Fixodent "investigational product" and caused zinc plasma levels to rise in all subjects (June 2013 Askari Report 16); (2) in PK Study 2, the zinc plasma levels in 90 percent of the subjects remained elevated after eight hours, "and elevated zinc plasma over a period of hours makes Fixodent users even more susceptible to copper deficiency because the product is ingested over the course of the use of the product" (*id.* 16, 18); (3) some of the subjects who received a single bolus dose of Fixodent exhibited elevated zinc plasma levels on par with subjects who have been put into a negative copper balance with Galzin (*see id.* 19).

Assuming the relevancy of the PK Studies based on Plaintiffs' experts' new analysis, the Court must determine whether Plaintiffs' experts' opinions are reliable. The correction factors employed by the PK Studies are the primary point of contention between the parties and are critical to their differing interpretations of the studies' results. In short, Defendants' experts rely on the corrected data; Plaintiffs' experts do not. Because Plaintiffs' experts intend to use the uncorrected raw data from the PK Studies, the Court focuses its *Daubert* inquiry on that decision.

Both Plaintiffs' and Defendants' experts agree zinc serum levels rise and fall throughout the day. As Dr. Askari notes, "It is well-accepted in the scientific literature that zinc plasma levels in humans fluctuate over the course of 24 hours. This has been described as a natural

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Fixodent to 25mg as zinc acetate is an unfair comparison." (June 2013 Smith Report 62).

circadian rhythm of zinc." (June 2013 Askari Report 24 (citation omitted)). "High basal levels in the morning are followed by a low natural decline throughout the day." (*Id.* 14; *see also* Johnson Report 4 ("It is known that zinc concentrations in the blood rise and fall throughout a 24-hour day. The change in zinc level is a normal circadian rhythm that is similar to the daily variations that occur with other physiological functions."); Grainger Report 5 ("Baseline determinations for plasma zinc in humans have a history of high daily variance.")).

Dr. Askari testified that correcting the baseline is the only scientifically viable way to conduct pharmacokinetic studies. (*See* January 20, 2012 Deposition of Frederick Askari ("2012 Askari Deposition Transcript") 248:9–19 [ECF Nos. 2197-29, 30]). An example of this generally accepted scientific practice is a study conducted by Plaintiffs' former expert, Dr. George J. Brewer, evaluating the effect of intragastric pH on the absorption of zinc, where "Plasma zinc concentrations for hour 1 through hour 8 were adjusted for baseline zinc concentration by subtracting the hour 0 concentration value." Lisa M. Henderson, *et al.*, *Effect of Intragastric pH on the Absorption of Oral Zinc Acetate and Zinc Oxide in Young Healthy Volunteers*, J. OF PARENTERAL & ENTERAL NUTRITION, Sept. 1995, 393–397, 395.

Recognizing the importance of creating a baseline measurement in this instance, Dr. Askari proposed a proper method for establishing a baseline in the PK Studies would have been to bring the "subjects to a study center, place them on a controlled zinc diet for a sufficient period of time to establish a normal baseline of zinc plasma in each subject, and [] test the subject's zinc plasma level at time-matched intervals during 24 hours." (June 2013 Askari Report 24). Dr. Askari also cites another study that advocates the use of different basal levels at different times of the day to account for the fluctuation in serum zinc levels. (*See id.* 14 (citing J. Neve, *et al.*, *Pharmacokinetic Study of Orally Administered Zinc in Humans: Evidence for an*

Eternal Recirculation, EUR. J. DRUG METABOLISM AND PHARMACOKINETICS, Feb. 11, 1991, 315–23, 316 ("The basal value was then corrected at each examined time for the physiological circadian variation in plasma zinc . . . Increases in zinc concentrations due to supplementation were finally obtained by subtracting the corrected basal level from the measured value." (alteration added))).

To account for this fluctuation, the PK Studies employed correction factors to subtract baseline levels of endogenous zinc already in the body from zinc attributable to Fixodent or zinc acetate. As Defendants' expert, Dr. Johnson, explains, "[i]t is critical that the determination of zinc bioavailability from Fixodent and Galzin not be confounded by the inclusion of zinc levels that are already in the blood. Without the correction, the result would give a false value that reduced the relative bioavailability of zinc from Fixodent compared to zinc from Galzin."[27] (Johnson Report 4).

Plaintiffs' experts challenge the validity of the correction factors employed in the PK Studies. In Dr. Askari's opinion, the baseline correction factor applied in PK Study 1 rendered the corrected values fundamentally flawed. (*See* June 2013 Askari Report 24). Dr. Smith believes the corrected values "introduce[] unacceptable bias into the analysis and raise[] questions about the validity of the baseline correction." (June 2013 Smith Report 62 (alterations added)).

Dr. Askari thus examines the uncorrected zinc plasma levels from the PK Studies, examines individual data points, discusses both the corrected and uncorrected values, and draws

[27] In PK Study 1, baseline plasma zinc levels were calculated by averaging the plasma zinc level just before dosing with the plasma zinc level 24 hours earlier. (*See* Johnson Report 4). The calculated baseline plasma zinc level was subtracted from the plasma zinc levels post-dosing. (*See id.*). In PK Study 2, baseline plasma zinc levels were determined from blood samples taken 24 hours before blood was drawn post-dosing. (*See id.* 5).

conclusions from both. (*See* June 2013 Askari Report 14–19). Dr. Askari's approach to the data reflects his awareness of the circadian rhythm of the body's zinc plasma levels; this was even described in his report. While it may not be in accordance with generally accepted practice — as reflected by Dr. Askari's own recognition of the importance of correction factors and citation to studies employing correction factors — any flaws in Dr. Askari's conclusions based on the use of the uncorrected serum zinc values "are of a character that impugn the accuracy of his results, not the general scientific validity of his methods." *Quiet Tech. DC-8, Inc.*, 326 F.3d at 1345.

The Court has concerns, however, about the reliability of Dr. Smith's use of the uncorrected serum zinc values. In analyzing the PK Studies and making his calculations regarding the bioavailability of zinc in Fixodent, Dr. Smith does not mention or recognize the body's inherent fluctuations in serum zinc levels, he does not explain the relevance of the correction factors, and he does not attempt to adjust his opinion to account for the fact the uncorrected raw data contains an uncertain amount of preexisting zinc in the body not attributable to the administered Fixodent. (*See* Johnson Report 18). *See Claar v. Burlington N. R.R. Co.*, 29 F.3d 499, 502 (9th Cir. 1994) (affirming exclusion of testimony where expert, *inter alia*, failed to consider other obvious causes for the plaintiff's condition); *Ballard*, 2011 WL 474814, at *5 (finding expert's failure to consider obvious alternative explanations weighed against the admissibility of his testimony (citing Rule 702 advisory committee's note (2000 amends.))). Dr. Smith's dismissal of an obvious factor indicating the bioavailability of zinc might be lower than he calculates starkly contrasts his willingness to consider "real life usage" factors he cursorily mentions and speculates makes the bioavailability of zinc in Fixodent "probably considerably higher and more likely than not approach[ing] 100%." (June 2013 Smith Report 64 (alteration added)).

If Defendants' corrected baseline values are biased, so, too, is Dr. Smith's opinion, which is based on incomplete and selective evidence and reflects an attempt to make the available data support Plaintiffs' opinion that the zinc in Fixodent is as bioavailable as zinc acetate.[28] *See Rink*, 400 F.3d at 1293 n.7 ("In evaluating the reliability of an expert's method . . . a district court may properly consider whether the expert's methodology has been contrived to reach a particular result." (alteration added)). Dr. Smith's calculation that the zinc in Fixodent is 80 to 100 percent bioavailable is inadmissible.

* * *

To summarize the clinical trial findings: the Fixodent Blockade Study is inadmissible and, consequently, Plaintiffs still have no evidence of the zinc in Fixodent's ability to inhibit copper absorption at the relevant site of action — the intestines; Dr. Grainger's conclusions based on the *in vitro* studies are also inadmissible; the results of the unpublished PK Studies show, at best, an uncertain amount of Fixodent becomes bioavailable, as reflected in serum zinc levels — but ultimately, the PK Studies show Fixodent is *not* as bioavailable as the Galzin in zinc acetate and taking more and more Fixodent may not expose a person to more and more zinc. In short, Plaintiffs are not much better off than they were at the time of *Chapman*.

In light of these conclusions, the Court finds Plaintiffs cannot reliably infer from Wilson Disease research how much Fixodent is necessary to consistently induce a negative copper balance. Moreover, as the undersigned noted in *Chapman*, the Wilson Disease research still leaves a large analytical gap between the proposition that a 25-milligram dose of zinc may place

[28] Dr. Smith's reliance on selective and favorable data is apparent from the fact he did not include in his report that there were no changes from baseline in the corrected and uncorrected plasma concentrations of copper, and that PK Study 1 found there was no change in ceruloplasmin levels. (*See* Sept. 2012 Smith Dep. Tr. 94:17–95:13; 96:2–8).

a particular person into a negative copper balance and the proposition that person will develop copper deficiency and severe copper deficiency with neurological symptoms, or CDM.[29] As discussed below, Plaintiffs' dose-response evidence does not fill this gap.

Other than the Fixodent Blockade Study, the *in vitro* studies, and the PK Studies, there are no other Fixodent-specific clinical studies. None of these existing clinical studies are dispositive of the ultimate question whether Fixodent can cause CDM. Plaintiffs' experts are not aware of any clinical studies demonstrating Fixodent can induce even a copper deficiency. (*See* Sept. 2012 Smith Dep. Tr. 34:4–8).

3. Analytical Epidemiological Evidence & Background Risk of Disease

Epidemiology is "generally considered to be the best evidence of causation in toxic tort cases." *Kilpatrick*, 613 F.3d at 1337 n.8 (citation omitted).

> Epidemiology is the field of public health and medicine that studies the incidence, distribution, and etiology of disease in human populations. . . . 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. Epidemiology focuses on the question of general causation (i.e., is the agent capable of causing disease?)

Green, REFERENCE MANUAL 3d ed. 551–52 (alterations added).

There are two classes of epidemiological evidence: analytical and descriptive. *See In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d at 1353–54 (citing March 24, 2011 Expert Report of Ebbing Lautenbach ("2011 Lautenbach Report") ¶ 42 [ECF No. 1046-9]). Analytical evidence consists of randomized controlled trials, case control studies, and cohort studies, while descriptive evidence consists of case studies and case series. *See id.* In contrast to the argument

[29] Plaintiffs' experts also admit the Wilson Disease experience does not provide analytic evidence that a zinc-infused negative copper balance will lead to copper deficiency. (*See* April 26, 2013 Deposition of Martyn Smith ("2013 Smith Deposition Transcript") 115:17–21 [ECF No. 2197-41]).

presented in *Chapman*, Plaintiffs claim they now have analytical epidemiological evidence to support their theory of general causation — Dr. Lautenbach's cohort study, developed using the previously discussed Gabreyes Study.

"In cohort studies, researchers define a study population without regard to the participants' disease status. The cohort may be defined in the present and followed forward into the future (prospectively) or it may be constructed retrospectively as of sometime in the past and followed over historical time toward the present. In either case, the researchers classify the study participants into groups based on whether they were exposed to the agent of interest []." Green REFERENCE MANUAL 3d ed. 557 (alteration added; footnote call number omitted). In a retrospective study, as in this instance, "the researcher will determine the proportion of individuals in the exposed group who developed the disease from available records or evidence and compare that proportion with the proportion of another group that was not exposed. . . . If the exposure causes the disease, the researcher would expect a greater proportion of the exposed individuals to develop the disease than the unexposed individuals." (*Id.* at 557–58 (alteration added)). As always, the "temporal relationship is critical to the question of causation, because exposure must precede disease onset if exposure caused the disease." (*Id.* at 558).

According to Dr. Lautenbach, the 2012 Gabreyes Study "represents a significant advance in the epidemiologic evidence for an association between denture cream use and CDM." (2013 Lautenbach Report ¶ 6). Dr. Lautenbach admits the Gabreyes Study is not, in and of itself, an analytic epidemiology study because it did not have a comparison group. (*See* June 4, 2013 Deposition Transcript of Ebbing Lautenbach ("2013 Lautenbach Deposition Transcript") 114:14–115:6 [ECF No. 2197-35]). Rather, the Gabreyes Study is a "retrospective 5-yr (2005–2010) review of all patients in Scotland biochemically identified as copper deficient," and

involved the assessment of the subjects' "haematological and neurological symptoms and signs, to further characterize the condition and identify signs that might prompt early treatment." (Gabreyes Study 2).

The authors used information from a national reference laboratory, the Scottish Trace Element and Micronutrient Reference Laboratory ("STEMRL"), that performs copper analyses. (*See id.*). The authors defined copper deficiency, or hypocupremia, as serum copper level <6 μM/L.[30] (*See id.*). The authors chose this value based on a prior study, explaining the "median copper value found in Halfdanarson's study was 3.6 uM, and so we expected to detect all relevant clinical cases without including a large number of milder asymptomatic cases of hypocupremia." (*Id.*).

The authors approached the clinician in charge of the identified copper-deficient patients for clinical history and examination, and the "cause of hypocupremia with any associated zinc supplementation, duration from first presentation to diagnosis and responses to treatment were assessed." (*Id.*). A total of 22 patients with low serum copper were identified from this five-year period, but only 16 were included in the final analysis because notes for four patients were not available and the clinician in charge of two patients declined to admit these patients to the study. (*See id.*). Twelve of the 16 patients had high serum zinc concentrations, nine of which were noted to be "due to zinc-containing dental fixatives." (*Id.*). Of the 16 patients, 12 had both haematological and neurological features of copper deficiency. (*See id.*).

All patients were given oral copper replacement, resulting in the improvement of serum copper levels to normal, except in one patient who continued to use zinc-containing dental fixative. (*See id.* 7). Of the 12 patients with both haematological and neurological features of

[30] In another part of the Gabreyes Study, the authors use ≤6 μM/L. (*See* Gabreyes Study 2).

copper deficiency, three had partial improvement in their sensory and motor symptoms, four deteriorated, and five showed no significant change. (*See id.*).

According to the Gabreyes authors, the "study demonstrates that copper deficiency is an under-recognized cause of several types of cytopenia," which, if left untreated, "can progress to significant neurological injury." (*Id.* 1). The authors also note the study "highlights the association between long-term zinc exposure through dental fixatives and the subsequent haematological and neurological symptoms and signs described elsewhere." (*Id.* 8).[31]

Dr. Lautenbach, an epidemiologist and treating physician, used the Gabreyes Study as the foundation for his retrospective cohort study. In his study, Dr. Lautenbach calculated the incidence of CDM among the population that uses zinc-containing denture cream, and the incidence of CDM among the population that does not use zinc-containing denture cream. Dr. Lautenbach compared the two incidence rates and concluded the risk of CDM in the population exposed to zinc-containing denture cream is, at a minimum, eight times greater, and possibly as high as 54 times greater, than the risk faced by the general population.[32] (*See* Opp'n 3–4; 2013 Lautenbach Report ¶¶ 26, 33).

Dr. Lautenbach began his study by calculating the number of denture wearers in Scotland who use denture cream. Using recent census data that the Scottish population is approximately 5.2 million, together with data from Procter & Gamble providing approximately 21 percent of

[31] As previously discussed, the "elsewhere" the Gabreyes Study references are two articles, one which relies on the Nations and Hedera case series the Court previously found suffered from a number of flaws and methodological weaknesses, and the other which contains no mention of denture adhesives. (*See* 2013 Nelson Report 17 n.14).

[32] The background risk of a specific disease is "the risk that everyone faces of suffering the same malady that a plaintiff claims without having exposure to the same toxin. . . . The background risks include all those causes of a disease, whether known or unknown, excluding the drug or chemical in question." *McClain*, 401 F.3d at 1243 (alteration added).

the United Kingdom population wears dentures, Dr. Lautenbach estimated the proportion of the Scottish population that wears dentures is approximately 21 percent, or 1.09 million. (*See* 2013 Lautenbach Report ¶¶ 20–22).

Next, Dr. Lautenbach calculated the proportion of Scottish denture wearers who use denture cream. Data from Procter & Gamble documents show six to seven percent of denture wearers in the United Kingdom use denture cream, compared to 27 to 41 percent in the United States. (*See id.* ¶ 23). Based on this data, Dr. Lautenbach estimated 25 percent of denture wearers in Scotland use denture cream, and thus, the number of exposed subjects (denture wearers who use denture cream) is approximately 0.27 million (1.09 million x 0.25) Scottish residents, and the number of unexposed subjects (those who either do not wear dentures or wear dentures but do not use denture cream) is approximately 4.93 million. (*See id.*).

Dr. Lautenbach used his calculated population statistics in combination with the results of the Gabreyes Study to determine the incidence of CDM in the exposed and unexposed populations. The Gabreyes Study reported 12 of the 16 patients had high serum zinc concentrations, nine of which were "due to zinc-containing dental fixatives." (Gabreyes Study 2). It also reported 12 of the 16 patients had both haematological and neurological features of copper deficiency. (*See id.*). The study did not provide information regarding the overlap between these patients, but Dr. Lautenbach calculated as many as nine and as few as six subjects were both denture cream users and exhibited haematological and neurological symptoms of copper deficiency, which he considers to be CDM. (*See id.* ¶ 17). Using these two figures, Dr. Lautenbach calculated two possible incidence rates of CDM.

Using the higher nine-subject figure in his calculations, Dr. Lautenbach concluded there is an incidence rate ratio of 54.78, and thus a statistically significant incidence of CDM among

denture cream users in Scotland compared to non-denture cream users. (*See id.* ¶¶ 24–26). Using the lower six-subject figure in his calculations, Dr. Lautenbach concluded there is an incidence rate ratio of 18.26, and thus a statistically significant incidence of CDM among denture cream users in Scotland compared to non-denture cream users. (*See id.* ¶ 27).

As part of his sensitivity analysis, Dr. Lautenbach repeated his calculation of the incidence rate of CDM for a second time, changing the assumption that 25 percent of denture wearers in Scotland use denture cream to an assumption that 50 percent of denture wearers in Scotland use denture cream. (*See id.* ¶ 29). Based on this changed assumption, Dr. Lautenbach concluded there remains a statistically significant greater incidence rate — as much as 25 and as little as eight — of CDM among denture cream users in Scotland compared to non-denture cream users. (*See id.* ¶¶ 29–33).

As part of his cohort study, Dr. Lautenbach opined his calculations of the incidence rate of CDM in the Scottish population are generalizable to the U.S. population. This extrapolation is based on Dr. Lautenbach's comparison of the size of the Scottish and U.S. populations (5.2 million and 314.0 million, respectively), and observations the two populations have similar sex, age, and race distributions. (*See id.* ¶ 34). Dr. Lautenbach also considered the proportions of Scottish and U.S. populations wearing dentures to be comparable, based on his previous estimate that 21 percent of the Scottish population wears dentures, and data from Procter & Gamble showing 24 percent of the U.S. population wears dentures. (*See id.* ¶ 35). Dr. Lautenbach concluded his cohort study confirms the existing evidence supporting a causal relationship between the zinc compound in Fixodent and CDM. (*See id.* ¶ 36).

The Court, in performing its *Daubert* review, must examine each step in Dr. Lautenbach's logic to be assured of the scientific reliability of Dr. Lautenbach's conclusions. To

begin, Dr. Lautenbach draws several conclusions that go beyond those made by the Gabreyes Study authors themselves. Most notably, Dr. Lautenbach treats each of the 12 patients noted in the Gabreyes Study to exhibit both haematological and neurological features of copper deficiency as being diagnosed with CDM, even though the Gabreyes authors never mention CDM. (*See* 2013 Lautenbach Report ¶ 15; *see generally* Gabreyes Study).

The authors of the Gabreyes Study were not performing contemporaneous "clinical research," but rather an "observational" "audit . . . based on retrospective review of case records" from 2005–2010. (Discovery Response prepared by Gabreyes author, Ian Morrison ("Gabreyes Author Response") [ECF No. 2194-16] (alteration added)). The authors admit it "is not known to what extent the treating clinician applied consistent case definitions and/or diagnostic criteria in management of their patients," and they "did not appraise the case definitions or diagnostic criteria of the treating clinician." (*Id.*). Consistent with their review, the Gabreyes authors did not conclude these patients had CDM. It is thus unclear how Dr. Lautenbach did, particularly when he did not perform any independent review of patient records. (*See* 2013 Lautenbach Dep. Tr. 104:16–105:11).[33]

The Gabreyes Study also does not support Dr. Lautenbach's conclusion that zinc-containing denture cream causes CDM. The Gabreyes Study makes the following statements about denture cream usage: "nine patients were using zinc-containing dental fixatives at the time of diagnosis" of high serum zinc (Gabreyes Study 1); nine patients "had high serum zinc concentrations (>18 μM/L) due to zinc-containing dental fixatives" (*id.* 2); "All patients who had severe neutropenia leading to bone marrow investigation also had significant neurological

[33] The assumption that these patients had CDM is also called into question where the condition of four of these patients deteriorated, and five showed no significant change, after oral copper replacement therapy was initiated and zinc exposure was removed. (*See* Gabreyes Study 7).

complaints, and all were using zinc-containing denture fixatives" (*id.* 6); "In all our patients, the replacement of copper sulphate at 2.5 mg twice daily dose . . . resulted in improving the serum copper level to normal except in one patient who continued to use zinc-containing dental fixative" (*id.* 7 (alteration added)); and, finally, the authors' claim their review "highlights the association between long-term zinc exposure through dental fixatives and the subsequent haematological and neurological symptoms and signs" (*id.* 8).

The one causal statement in the Gabreyes Study pertains to denture cream usage and high serum zinc concentrations, not copper deficiency or CDM. (*See id.* 2). The other statements merely note a temporal association. Although a "temporal relationship is critical to the question of causation . . . exposure *must* precede disease onset if exposure caused the disease." Green REFERENCE MANUAL 3d ed. 558 (alteration and emphasis added); *see Hendrix*, 609 F.3d at 1197 ("Thus, a mere temporal relationship between an event and a patient's disease or symptoms does not allow an expert to place that event on a list of possible causes of the disease or symptoms.").

Furthermore, the Gabreyes Study fails to provide information necessary to reliably conclude a causal relationship exists between zinc-containing denture creams — Fixodent in particular — and copper deficiency or neurological injury. It provides no information on the amount of denture cream use, length of use, brand used, or, most importantly, whether the dental cream exposure preceded the copper deficiency or onset of neurological symptoms. (*See generally* Gabreyes Study). The Gabreyes authors, who reviewed the medical files of the 16 study subjects, admitted they did not examine information specific to denture cream usage as part of their audit. (*See* Gabreyes Author Response). The authors also did not analyze or assess other illnesses that may have caused the reported copper deficiencies. (*See id.*). According to the authors, the observations included in the study suggesting the cause of copper deficiencies

were "exclusively based on the opinion of the treating clinicians." (*Id.*).[34]

Dr. Lautenbach's cohort study does not account for the lack of information pertaining to the subjects' denture cream usage, and it is based on the assumption this information was appropriately taken into account by the underlying treating physicians. According to Plaintiffs, "all of the Gabreyes study subjects whose treating physicians attributed the *cause* of their copper deficiency to their use of zinc-containing denture cream clearly began using denture cream prior to the onset of their injuries, lest that diagnosis could not have been made." (Opp'n 41 (citing 2013 Lautenbach Dep. Tr. 109:19–110:1; 111:10–16) (emphasis in original)). Dr. Lautenbach also assumes the treating physicians took into account the amount of denture cream use, claiming it was "obviously a volume high enough [] to trigger that as a designation for physicians." (2013 Lautenbach Dep. Tr. 109:3–10 (alteration added); *see id.* 40). Finally, Dr. Lautenbach assumes the treating physicians must have accounted for alternative causes of copper deficiency, confounding factors, and biases. (*See* Opp'n 41; 2013 Lautenbach Dep. Tr. 217:4–218:12).

Although Plaintiffs say reliance on treating physicians' determinations is typical for clinical epidemiologic studies (*see* Opp'n 38), the extent of Dr. Lautenbach's reliance is a complete delegation of his responsibilities as an epidemiologist to assess the subjects' exposure

[34] The Gabreyes authors provided the following responses to Defendants' discovery requests after Dr. Lautenbach's cohort study was produced.

Asked "Whether, if so to what extent, by which method or methods and with what results the authors analyzed the denture cream used by the patients or assessed or measured the amount or type of cream so used," the authors stated, "this was not performed as part of the audit." (Gabreyes Author Response).

Asked "Whether, if so to what extent by which method or methods and with what results the authors analyzed or assessed whether there were underlying illnesses or other potential causes or reasons for the patients having neurological abnormalities, significant zinc concentrations, low copper concentrations and/or copper deficiency," the authors stated, "the audit was observational, based on retrospective review of case records. The authors did not analyze nor assess for other illnesses that may cause copper deficiency. The observations in the paper suggesting the cause of copper deficiency are exclusively based on the opinion of the treating clinician." (*Id.*).

to the dental cream, adjust for confounders, and account for bias.[35] With no corroboration from his own review of the medical records, or that of the Gabreyes Study authors, Dr. Lautenbach assumes the treating physicians, during the normal course of treating their patients, conducted a thorough analytical epidemiological assessment. This is the same assumption Plaintiffs make about denture cream case reports. If such an assumption was reliable, courts would not be so hesitant to rely on case studies as evidence of general causation. *See e.g.*, *Hendrix*, 609 F.3d at 1197 (finding case studies by themselves to be "insufficient to show general causation" (citations omitted)); *McClain*, 401 F.3d at 1254 ("[C]ase report raise questions; they do not answer them." (alteration added)); *Rider*, 295 F.3d at 1199 ("[C]ase reports are merely accounts of medical events. They reflect only reported data, not scientific methodology."); *Haggerty v. Upjohn Co.*, 950 F. Supp. 1160, 1165 (S.D. Fla. 1996) ("[W]hile case reports may provide anecdotal support, they are no substitute for a scientifically designed and conducted inquiry." (alteration added; citation omitted)).

As to the lack of information on the brand of denture cream used by the nine Gabreyes subjects, Plaintiffs claim the information is "of no consequence" because Fixodent and SuperPoligrip own the market for zinc-containing denture cream in Scotland, with Fixodent's market share at 45 percent; and, because Dr. Grainger's report shows SuperPoligrip and Fixodent dissociate the same way, these two brands should be treated the same. (*See* Opp'n 38–39). Plaintiffs' logic — that since Fixodent controls 45 percent of the market share, Fixodent must be responsible for 45 percent of the denture cream subjects in the Gabreyes Study — is faulty, and for reasons explained above, the Court does not find Dr. Grainger's report reliably supports the

[35] *See* Green, REFERENCE MANUAL 3d ed. 572 ("Three general categories of phenomena can result in an association found in a study to be erroneous: chance, bias, and confounding. Before any inferences about causation are drawn from a study, the possibility of these phenomena must be examined.").

conclusion that SuperPoligrip and Fixodent should be treated the same.

Defendants' challenge to the use of the Gabreyes Study to infer general causation also calls into question whether the authors identified "all cases of copper deficiency in Scotland" because annual reports published by STEMRL show other laboratories in Scotland conducted blood copper testing during the relevant time period. (*See* Mot. 24–25 (citing STEMRL annual reports from 2004 to 2011)). Dr. Lautenbach did not consider these annual reports (*see* 2013 Lautenbach Dep. Tr. 113:19–114:11; 225:11–226:3), and Plaintiffs continue to rely on the representations of the Gabreyes Study authors alone, dismissing the relevancy of the STEMRL annual reports as Defendants' "one-sided interpretation." (Opp'n 35).

In addition, Defendants argue the authors of the Gabreyes Study did not identify all cases of copper deficiency in Scotland because: as the authors themselves admit, copper deficiency is under-recognized and "actual prevalence is likely to be higher" (Gabreyes Study 8); an unknown number of people who potentially had copper deficiency were not included in the Gabreyes Study because the authors chose a restrictive definition — those with blood copper levels <6 μM/L[36] — even though the normal reference range is 10–22 μM/L; and six of the 22 patients (over 27 percent of the patients) who met the authors' definition of copper deficiency were excluded due to lack of physician consent or medical records. (*See* Mot. 27–29). Dr. Lautenbach's report does not discuss the implications of these restrictions or exclusions to his ultimate conclusion.

[36] Plaintiffs point to this <6 μM/L cutoff in support of their position that the Gabreyes authors used a case definition. (*See* Opp'n 30). It is not disputed this case definition was applied by the Gabreyes authors. However, the case definition does not contain a neurological component, such as the case definition applied *post hoc* by Dr. Lautenbach in his cohort study —"low serum copper concurrent with neurologic findings (i.e., neuropathy, myelopathy, or both)." (2013 Lautenbach Report ¶ 15). Without a proper case definition applied at the outset of the data collection, it is uncertain if all of the subjects with CDM were systematically identified.

The Court does not doubt the peer-reviewed Gabreyes Study is reliable in light of the study's stated purpose — to review cases of severe copper deficiency and "assess[] their haematological and neurological symptoms and signs, to further characterize the condition and identify signs that might prompt early treatment." (Gabreyes Study 2). Nonetheless, the study has severe limitations as a reliable foundation for building a cohort study to formally assess the association between zinc-containing denture cream and CDM. At its core, the basis for Dr. Lautenbach's cohort study is a summary of a collection of case reports, with severely inadequate information about denture cream usage. The layers of unsupportable estimations and approximations added to this already shaky foundation confirm the Court's finding that Dr. Lautenbach's cohort study is unreliable evidence of general causation.

Dr. Lautenbach employed two estimates in his calculation of the exposed population — the Scottish population that uses denture cream. The first estimate pertains to the proportion of the Scottish population that wears dentures. Because the number of denture wearers in Scotland has not been studied, Dr. Lautenbach relies on data from Procter & Gamble showing approximately 21 percent of the entire U.K. population wears dentures, to estimate 21 percent of the Scottish population, a subset of the United Kingdom, wears dentures. (*See* 2013 Lautenbach Report ¶ 22). Dr. Lautenbach provides no explanation for this transfer of data in his report and testified he does not have any data indicating whether the rates of endentulism, denture use, and denture adhesive use are the same in the rest of the United Kingdom as in Scotland. (*See* 2013 Lautenbach Dep. Tr. 204:9–16).

Plaintiffs explain, "[w]ith Scots representing only 8.16% of the U.K. population, the majority of denture cream users in the U.K. are likely not in Scotland, and, in any event, the population is likely to be far less than the 21% estimate that Dr. Lautenbach used." (Opp'n 53

(alteration added)). This explanation confirms Dr. Lautenbach's estimate was not based on "particularized findings which accounted for the differences in conditions" between the whole of the United Kingdom and Scotland. *Rink*, 400 F.3d at 1290. "Transposition of data based on such conjecture and rough approximation lacks the intellectual rigor required by *Daubert*." *Id.* at 1292 (internal quotation marks and citation omitted).[37]

Dr. Lautenbach's second estimate is layered on top of the unreliable first estimate in order to calculate the proportion of the Scottish denture-wearing population that uses denture cream. Dr. Lautenbach estimates 25 percent of denture wearers in Scotland use denture cream, and then, as part of his sensitivity analysis, performs his calculations a second time using a 50 percent figure. (*See* 2013 Lautenbach Report ¶¶ 23, 29). Although Dr. Lautenbach claims his calculations are "based on" Procter & Gamble literature, it is not entirely clear how: Procter & Gamble data show the proportion of denture wearers that uses denture cream is six to seven percent in the United Kingdom, and 27 to 41 percent in the United States. (*See id.* ¶ 23). Dr. Lautenbach's estimated percentages do not reflect the data, and he fails to demonstrate he used any principles or methods to arrive at his estimates, let alone reliable ones. *See Placida Prof'l Ctr. v. FDIC*, No. 8:09-cv-2221-T-30MAP, 2011 WL 5975268, at *7 (M.D. Fla. Oct. 18, 2011) (rejecting expert testimony that "fail[ed] to explain the precise methodology utilized to derive his 28 percent figure, after having settled on a . . . range of 20% to 60%." (alterations added)).

[37] In response to Defendants' argument the U.K. data Dr. Lautenbach used pre-dated the Gabreyes Study period by over a decade, Plaintiffs present more recent evidence — not cited by Dr. Lautenbach in his report — showing the 21 percent figure is still accurate. (*See* Opp'n 52–53). Plaintiffs also point to evidence, cited by Defendants' expert Dr. Nelson, to show the total population of all persons age 16 and over without teeth in Scotland is only 12 percent, "far less than the 21 percent that Dr. Lautenbach used for his estimate." (Opp'n 53). This after-the-fact attempt to bolster Dr. Lautenbach's opinion does not instill confidence in Dr. Lautenbach's methodology. Indeed, it seems to highlight the fact Dr. Lautenbach failed to conduct a thorough review of relevant data or base his estimates on reliable evidence in the first place.

Furthermore, the percentages Dr. Lautenbach uses to calculate his exposed population include users of all brands of denture cream and do not distinguish between denture wearers using zinc-containing denture cream versus other formulations. (*See* 2013 Nelson Report 31). In light of his use of unsupported assumptions and factually inaccurate data, Plaintiffs' assurances that Dr. Lautenbach employed a "sensitivity analysis" based on generally accepted methodology used by epidemiologists are insufficient. *See McClain*, 401 F.3d at 1244 (finding expert's attempts to "anoint his opinions by claiming that he based them on the 'broad principles of pharmacology'" had little value in the *Daubert* context).

Dr. Lautenbach, in his cohort study, and Plaintiffs, in their opposition brief, repeatedly insist the figures used in the cohort study are conservative estimates and assumptions, the actual proportion of denture cream users is likely much lower, and the results of the study are, if anything, skewed in Defendants' favor. (*See* 2013 Lautenbach Report ¶¶ 23, 32; Opp'n 49, 54). Such statements, presumably meant to imply Defendants will not be prejudiced if the study is admitted, in fact have the opposite effect. Whether or not the results are "skewed" in Defendants' favor does not remedy the fact they were arrived at using cherry-picked data and flawed methodology. Taken together with the Court's review of the Gabreyes Study, the Court finds Dr. Lautenbach's cohort study is inadmissible.[38]

[38] Prior to developing his cohort study, Dr. Lautenbach provided a study published in the United Kingdom in 2000, the "MacDonald Study," as evidence of the background rate of myelopathy. (*See* August 30, 2012 Supplemental Expert Report of Ebbing Lautenbach ("August 2012 Lautenbach Report") [ECF No. 2194-1])). The authors of the MacDonald Study set about over an 18-month period to conduct an analysis of the incidence and lifetime prevalence of neurological disease in the United Kingdom. (*See id.* 1).

The MacDonald study, however, does not identify any of the neurological conditions as a myeloneuropathy, let alone a copper deficiency myeloneuropathy. In an attempt to extrapolate relevant findings from this data, Dr. Lautenbach combines the "extremely low rates of idiopathic myelopathy" found in the study, with "the rate of motor neuron disease," which he claims is "often described in patients suffering from zinc induced copper deficiency neurological disease," for a combined incidence rate that is "extremely low (i.e., approximately 4 per 100,000)." (*Id.*).

* * *

Without Dr. Lautenbach's cohort study, Plaintiffs continue to have no analytical epidemiological evidence on which to base their inference of causation. In the absence of any analytical epidemiological studies, "the nature of the other evidence . . . becomes that much more important, and the court's consideration of such evidence and the methodologies used must be that much more searching." *Kilpatrick*, 613 F.3d at 1337 n.9.

The absence of background risk of CDM also remains a substantial weakness in Plaintiffs' experts' causal reasoning. As noted in *Chapman*, "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. . . . Without a baseline, any incidence may be coincidence." *In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d at 1356.

4. Dose-Response Relationship

"When analyzing an expert's methodology in toxic tort cases, the court should pay

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According to Plaintiffs' own experts, however, the two conditions Dr. Lautenbach relies on are not even consistent with CDM: Dr. Greenberg testified the clinical presentation of motor neuron disease is much different than CDM and, "Idiopathic isn't a condition; idiopathic means 'I don't know.' There's no such thing as an idiopathic myelopathy." (November 29, 2012 Deposition Transcript of Steven A. Greenberg 188:11–190:16; 185:24–186:2 [ECF Nos. 2197-37, 38]).

Dr. Lautenbach also relied on a United States National Health Survey from 1976–1980 to try to address the proportion of the U.S. population that could be expected to have high zinc and low copper. (*See* Aug. 2012 Lautenbach Report 1). The values reported in this survey are not linked to excess zinc ingestion or copper deficiency. Further, tests from over thirty years ago are not a reliable indicator of how high blood zinc or low blood copper are today, as the intake of zinc through non-dietary routes has increased significantly. (*See* 2013 Nelson Report 24 (citing Sept. 11, 2012 Brewer Dep. Tr. 461:11–462:3)).

These studies are not reliable bases from which to infer that Fixodent can cause CDM. As evidence of such, these studies were not relied on by any of Plaintiffs' general causation experts. (*See* June 2013 Smith Report 67–69 (relying on the cohort study only); June 2013 Askari Report 25–29 (relying on the cohort study only); *see generally* Grainger Report; April 30, 2012 Expert Report of Steven A. Greenberg [ECF No. 2194-2]; August 30, 2012 Expert Report of Steven A. Greenberg [ECF No. 2194-3]).

careful attention to the expert's testimony about the dose-response relationship. 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 (internal quotation marks and citation omitted). "'[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.* at 1242 (quoting Eaton 16 (quoting CASARETT AND DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS Chs. 1, 4 (McGraw Hill 6th ed. 2001))). "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 Eaton 13). This "is almost certainly true of Fixodent, which, as even Plaintiffs concede, is safe when used in moderate amounts." *In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d at 1352.

In the *Chapman Daubert* Order, the Court found "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 1353. Plaintiffs' reliance on Wilson Disease research alone was insufficient because, while the research "establish[ed] what dose of Galzin, or zinc acetate, is necessary to induce a negative copper balance," the PK Studies suggested the zinc in Fixodent was less bioavailable than zinc acetate, and further, there was "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." *Id.*

Plaintiffs claim Drs. Smith, Askari, and Grainger offer new dose-response analyses and can identify the amount and duration of exposure from the zinc compound in Fixodent that will cause copper deficiency and resulting haematological and neurological injuries. (*See* Opp'n 3, 88). The Court addresses each in turn.

a) Dr. Smith

Dr. Smith provides several opinions Plaintiffs argue are evidence of a dose-response relationship. Dr. Smith's first opinion is based on an individual consuming zinc in excess of the daily upper limit established by the Institute of Medicine ("IOM"), a branch of the National Academy of Sciences. (*See* June 2013 Smith Report 4–5). The upper limit ("UL") established by the IOM for regular intake of zinc from all sources is 40 milligrams per day. (*See id.* 4). According to Dr. Smith, a consumer would need to apply approximately 2.44 to 3.56 grams of Fixodent to dentures per day to exceed the IOM upper limit, and thus 10 percent of Fixodent users are at risk of exceeding the IOM's upper limit. (*See id.* 5). Dr. Smith claims "Dose-response analysis shows that total zinc intake in excess of 40 mg/day can put people at risk of a copper deficiency and . . . over the course of several months to years (temporality) this copper deficiency may lead to toxic sequelae later in some users. These sequelae include anemia and myelopathy." (*Id.* 12 (alterations added)).

Dr. Smith's calculation of the percentage of Fixodent users at risk of exceeding the IOM's upper limit is articulated in his report. Dr. Smith's calculations begin with reports estimating the average daily zinc intake through diet in the United States to be between five to 16 milligrams. (*See id.* 4–5, 23). Based on this average daily zinc intake range, to exceed the IOM upper limit of 40 milligrams per day, Dr. Smith determines a denture cream user would have to

ingest between 24 to 35 milligrams of zinc from Fixodent. (*See id.* 4–5). According to Dr. Smith, a consumer would need to apply approximately 2.44 to 3.56 grams of Fixodent to the dentures per day to exceed the IOM upper limit. (*See id.* 5). He calculates this figure using Procter & Gamble internal studies showing consumers ingest upwards of 74.1 percent of the Fixodent they apply to their dentures, along with the previously discussed Procter & Gamble and GlaxoSmithKline *in vitro* studies demonstrating Fixodent's zinc dissociation properties, which the Court has ruled inadmissible. (*See id.* 5). His numbers are also based on his unreliable calculation that the zinc in Fixodent is 80 percent bioavailable based on the PK Studies. (*See id.*).

To review the reliability of the next step in Dr. Smith's opinion — that exceeding the IOM's upper limit for zinc intake can put people at risk for copper deficiency and ultimately lead to severe copper deficiency with myelopathy — the Court assumes the reliability of Dr. Smith's 80 percent bioavailability calculation as well as the reliability of Dr. Grainger's conclusions from the *in vitro* studies. Dr. Smith notes the IOM's upper level of 40 milligrams of zinc per day is in line with the No Observed Adverse Effect Level ("NOAEL") of 30 milligrams supplemental zinc per day, set by the Agency for Toxic Substances and Disease Registry ("ATSDR"). (*See id.* 26). "The ATSDR has estimated the exposure levels for zinc that pose a minimal risk to humans at Minimum Risk Levels (MRLs). An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects [] over a specified duration of exposure." (*Id.* (alteration added)). The MRL level for zinc was derived from a study identifying the highest NOAEL for effects of zinc exposure, the Yadrick study.[39] (*See id.*

[39] Yadrick M.K. et al., *Iron, Copper, and Zinc Status: Response to Supplementation with Zinc or Zinc and Iron in Adult Females*, 49 AM. J. OF CLINICAL NUTRITION 145–50 (1989).

27).

In the Yadrick study, a group of healthy adult women were exposed to 50 milligrams of zinc per day, in addition to their daily dietary consumption of zinc, for a total exposure level of 59.38 milligrams of zinc per day. (*See id.* 34). After the ten-week supplementation period, there was a decline in erythrocyte copper-zinc superoxide dismutase ("ESOD"), a biomarker of copper status, activity. (*See id.* 33–34). "By ten weeks, ESOD activity had declined to 53% of pretreatment levels." (*Id.* 34). The Yadrick study concluded "'supplementation of [zinc] with levels used in this experiment [50 mg] does indeed represent a risk with regard to . . . [copper] status.'" (*Id.* (quoting Yadrick study) (alterations added)).

The ATSDR also relied on the Fischer study, which tracked ESOD activity.[40] In this study, groups of 13 healthy adult male volunteers were instructed to take capsules containing either cornstarch — the control group, or 25 milligrams supplemental zinc — the test group, twice daily for six weeks. (*See id.* 34). For the group receiving the zinc capsules, taking into consideration their average daily dietary consumption of zinc, their total zinc exposure levels were 65.92 milligrams zinc per day. (*See id.* 34–35). At the end of the study, plasma copper levels did not change; however, ESOD activity decreased after four weeks in the zinc supplement group and was significantly lower than the control group by six weeks. (*See id.* 35). Based on the Yadrick and Fischer studies, Dr. Smith concludes "men as well as women, are at risk of copper deficiency from an additional 50 mg/day of zinc provided once or twice daily in 25 mg doses." (*Id.*).

Defendants challenge Dr. Smith's reliance on government-recommended zinc standards as a basis for inferring Fixodent is capable of causing copper deficiency and eventually a

[40] Fischer P.W.F. et al., *Effect of Zinc Supplementation on Copper Status in Adult Man*, 40 AM. J. OF CLINICAL NUTRITION 743–46 (1984).

myeloneuropathy if a consumer exceeds the standards. Defendants' expert, Dr. Johnson, explains,

> In establishing the intake levels for the UL, NOAEL and [Lowest Observed Adverse Effect Level], the Institute of Medicine took a conservative approach in recognition of the variability of the nutritional and medical circumstances of the public. None of these levels purport to establish a safety threshold above which clinical injury occurs. Importantly, they were not intended to, nor do they, support a dose response relationship between zinc ingestion and clinical injury.

(Johnson Report 3 (alteration added)).

The Eleventh Circuit has made a similar observation, cautioning reliance on public health rules as evidence of causation, because "'risk assessors may pay heed to any evidence that points to a need for caution, rather than assess the likelihood that a causal relationship in a specific case is more likely than not,'" and because "'a number of protective, often 'worst-case' assumptions . . . are made in estimating allowable exposures for large populations.'" *McClain*, 401 F.3d at 1249 (quoting Margaret A. Berger, in *The Supreme Court's Trilogy on the Admissibility of Expert Testimony*, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 33 (Federal Judicial Center, 2d ed. 2000); Eaton 34–35)).

As Dr. Johnson notes, the studies upon which these government-recommended levels are based, such as the Yadrick and Fischer studies, did not demonstrate hypocupremia, neurologic damage from chronic hyperzincemia-induced hypocupremia or other injury. (*See* Johnson Report 3). Further, these studies measured copper status by tracking the subjects' ESOD levels. Although the IOM considers ESOD to be "a sensitive indicator of the effect of high zinc levels on copper homeostasis," it states, "*the clinical significance of the depressed ESOD activity is unknown*." (Dietary Reference Intake 482 [ECF No. 2194-34] (emphasis added)).

The uncertainty of the association between ESOD levels and copper levels is also recognized by the ASDTR:

> Excessive dietary zinc has been shown to induce a reversible copper deficiency and anemia in experimental animals. Similar effects have been seen in humans receiving long-term treatment with zinc. However, no significant decreases in plasma copper levels were observed in humans receiving zinc for six weeks or six months . . . These findings suggest that superoxide dismutase may be a sensitive indicator of zinc-copper interaction. However, as not all studies of zinc supplementation have noted changes in superoxide dismutase levels, *the association is still not completely clear*.

Nickolette Roney, et al., *ATSDR Evaluation of the Health Effects of Zinc and Relevance to Public Health*, 22 TOXICOLOGY AND INDUS. HEALTH 423, 464 (2006) ("Roney Article") [ECF No. 2194-35] (emphasis and alterations added; internal citations omitted).

The ATSDR also calls the clinical significance of the zinc supplementation studies into question, noting, "Other studies of zinc-exposed subjects have not reported significant changes in copper status (Fischer *et al.*, 1984; Black *et al.*, 1988; Milne *et al.*, 2001); however, these studies have either evaluated male subjects, who are not as sensitive to changes in iron status, or have not evaluated serum ferritin." (Roney Article 463). Further, according to the ATSDR, "subjects in the zinc supplementation studies did not report increased frequencies of clinical signs or symptoms. The other changes in copper status across the studies evaluating zinc supplementation in the 50 mg/day range . . . are generally slight and of questionable clinical and biological significance," and "[t]he subclinical changes in copper status observed in the intermediate-duration studies of zinc supplementation (Fischer *et al.*, 1984; Yadrick *et al.*, 1989; Davis *et al.*, 2000; Milne *et al.*, 2001) *are considered non-adverse effects*." (*Id.* 474 (alterations and emphasis added)). Thus, while the zinc supplementation studies indicate a possible association between zinc and copper levels, the IOM and ATSDR are reserved in drawing conclusions as to causation. Dr. Smith, however, is not.

Dr. Smith acknowledges the ATSDR's finding that the decrease in ESOD levels observed in the zinc supplementation studies do not indicate anything of clinical significance, and he

acknowledges the ATSDR does not consider a decrease in ESOD levels puts a person at risk of developing copper deficiency or myeloneuropathy. (*See* Sept. 2012 Smith Dep. Tr. 76:7–77:12). Dr. Smith also could not cite a study that occurred after the date of the ATSDR's review of available literature that concluded depressed ESOD activity was of any clinical significance. (*See id.* 115:12–15). Moreover, Dr. Smith testified a decreased ESOD level "may not have any immediate clinical significance, but it is a biomarker of altered copper status, which can't be a good thing." (*Id.* 78:2–5).

Dr. Smith's testimony fails to reflect the intellectual rigor required under *Daubert*. Moreover, given the government's inherently conservative approach to dietary recommendations, and the unknown clinical significance of the zinc supplementation studies on which the government based its recommendation levels, Dr. Smith has not demonstrated consumption of zinc in excess of government recommendations is a reliable indicator of copper deficiency, let alone severe copper deficiency with neurological symptoms.

Dr. Smith's second dose-response opinion is based on "[t]he available published peer-reviewed case reports show[ing] that high-end Fixodent users who receive doses of 69 milligrams or more of zinc from Fixodent (use of >7 grams of Fixodent adhesive per day) are susceptible to zinc-induced copper deficiency leading to myelopathy." (June 2013 Smith Report 7 (alterations added)). Dr. Smith also notes the existence of GlaxoSmithKline research based on case reports estimating the time from first use of zinc-containing denture adhesives to copper deficiency with the onset of severe symptoms is on average seven years. (*Id.*). These figures appeared for the first time in Dr. Smith's April 30, 2012 expert report (*see* April 30, 2012 Expert Report of Martyn T. Smith ("April 2012 Smith Report") 7 [ECF Nos. 2197-11, 12]), and seem to be an attempt by Dr. Smith to come up with evidence of a dose-response relationship, after

admitting just three months earlier there were no studies testing a dose-response relationship between the use of Fixodent, or any denture cream, and neurological symptoms.[41]

Dr. Smith's conclusion that users who receive doses of 69-milligrams or more of zinc from Fixodent are susceptible to zinc-induced copper deficiency from Fixodent is mentioned once, at the very start of his report, under his summary of conclusions. (*See* June 2013 Smith Report 7). A 69-milligram figure appears connected with case reports in two of his charts. (*See id.* 25, 58). One chart, "Levels at Which Hematological and Neurological Injuries Develop," has a bar for "denture cream case reports (69 mgs)." (*Id.* 58).

Aside from the cursory account at the start of his report that the 69 milligram figure is based on "available published peer-reviewed case reports" (*id.* 7), Dr. Smith provides no explanation for how he arrived at this figure, no explanation if he was relying on case reports involving Fixodent,[42] and, generally, no assurance he based his calculations on case reports with adequate and reliable evidence of denture cream usage and reliable evidence that any neurological symptoms were due to denture cream usage. *See In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d at 1354 ("[T]his is not an appropriate instance to rely on case studies

[41] Dr. Smith's testimony is as follows:

> Q. And what is the dose-response relationship between the use of Fixodent and neurological symptoms?
> A. I'm not sure that that has been studied.
> Q. Has it been studied for any denture cream?
> A. Not that I'm aware of, no.

(January 12, 2012 Deposition of Martyn Smith ("January 2012 Smith Deposition Transcript") 91:12–21 [ECF No. 2197-39]).

[42] Dr. Lautenbach testified there is still only one case report involving an exclusive Fixodent user, and three other case reports involving concurrent Fixodent and SuperPoligrip use. (*See* January 27, 2012 Deposition of Ebbing Lautenbach ("January 2012 Lautenbach Deposition Transcript") 96:10–13 [ECF No. 2194-11]). As the Court previously discussed, there is no reliable basis for Plaintiffs' argument that all denture cream and zinc supplementation case reports should be treated alike.

because the case studies Plaintiffs' experts rely on suffer from a number of inaccuracies and methodological weaknesses that undermine their evidentiary value." (alteration added)). He also could not provide an explanation for his calculation at his deposition. (*See* 2013 Smith Dep. Tr. 110:2–12; 13:16–20). Without this information, neither Defendants nor the Court can adequately evaluate Dr. Smith's methods in arriving at his conclusions. *See Cook*, 402 F.3d at 1111 ("[A] trial court may exclude expert testimony that is 'imprecise and unspecific,' or whose factual basis is not adequately explained." (quoting *Frazier*, 387 F.3d at 1266) (alteration added))).

In one paragraph of Dr. Smith's report, he notes GlaxoSmithKline research estimating the time from first use of zinc-containing adhesives to diagnosis of symptoms of copper deficiency is on average seven years. (June 2013 Smith Report 7, 56–57). Plaintiffs point to this as additional evidence of a dose-response relationship. But Dr. Smith's cursory description of the GlaxoSmithKline studies does not explain what "symptoms" or "injuries" from copper deficiency he is referring to. (*Id.* 56–57). In his deposition, he did not provide any greater description, calling them "severe" and "life-threatening" symptoms. (*See* 2013 Smith Dep. Tr. 119:25–120:12). Based on this lack of detail, the Court can only assume these are symptoms related to the neurological injuries at issue in the case.

Although this is the first indication of the amount of time it might take for symptoms of copper deficiency to appear, it is not a reliable basis for determining a dose-response relationship for Fixodent and CDM. The GlaxoSmithKline research relies on case reports and adverse event reports, both of which are insufficient to show general causation. *See McClain*, 401 F.3d at 1250 ("Uncontrolled anecdotal information offers one of the least reliable sources to justify opinions about both general and individual causation."); *see also Hendrix*, 609 F.3d at 1197; *Rider*, 295 F.3d at 1199; *Haggerty*, 950 F. Supp. at 1165. Even "well-documented cases" like those Dr.

Smith claims the GlaxoSmithKline research relied on, "are not reliable enough, by themselves, to demonstrate the causal link the plaintiffs assert that they do because they report symptoms observed in a single patient in an uncontrolled context." *McClain*, 401 F.3d at 1254 (internal quotations and citations omitted).

According to Dr. Smith's report, the seven-year estimate was developed based on 70 cases, but of those 70 cases, only 43 had no obvious confounders; and, further, of those 43 cases, only 16 reported concurrent use of SuperPoligrip and Fixodent. (*See* June 2013 Smith Report 57). It is unclear how long the concurrent use was taking place and how much SuperPoligrip was being used compared to Fixodent. Moreover, the relevance and reliability of the seven-year estimate are even more questionable given the Court's finding that Plaintiffs' argument for the identical treatment of SuperPoligrip and Fixodent cases is not supported by reliable scientific evidence.

b) Dr. Askari

Dr. Askari opines, based on Wilson Disease research, that a 25-milligram dose of zinc delivered each day for 30 days can place a person into a temporary state of negative copper balance, and "copper blockage caused from zinc overload from a product like Fixodent, left untreated, will result in copper deficiency and resulting hematological and/or neurological injuries." (June 2013 Askari Report 8, 29). Based on a review of the clinical evidence, the Court has found Plaintiffs cannot reliably infer from Wilson Disease research how much Fixodent is necessary to consistently induce a negative copper balance.

Even assuming the Wilson Disease research is relevant, Dr. Askari's opinion leaves the same large analytical gap the Court previously noted between a temporary negative copper

balance and severe copper deficiency with neurological symptoms.[43] *See In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d at 1353. As Dr. Smith also testified, the Wilson Disease experience does not provide any analytic evidence that a zinc-infused negative copper balance will lead to copper deficiency. (*See* 2013 Smith Dep. Tr. 115:17–21).

c) Dr. Grainger

Consistent with Plaintiffs' imprecise approach to general causation evidence, Plaintiffs include Dr. Grainger as a dose-response expert. Yet, Dr. Grainger has no opinion regarding copper, copper retention, copper deficiency and zinc, or neurological effects of copper. (*See* Grainger Dep. Tr. 68:11–69:15). Dr. Grainger's report simply states the application of two standard 68 gram tubes of Fixodent or more per week may expose a user to at least 330 milligrams of zinc per day, in excess of government recommended daily allowances. Viewed in the context of his report, this statement simply supports Dr. Grainger's argument that a single-dose PK/PD adhesive study does not accurately reflect real-life denture cream usage. (*See* Grainger Report 3–4). His opinion makes no attempt to connect the act of exceeding government recommended daily allowances for zinc with copper deficiency or CDM. Also, for the same reasons discussed in relation to Dr. Smith's dose-response opinion, consumption of zinc in excess of government recommendations is not a reliable indicator of copper deficiency or CDM.

* * *

In *Chapman*, "Plaintiffs' experts conclude[d] extremely large amounts of Fixodent applied to dentures several times a day for a period of many years can cause copper-deficiency

[43] This gap is also noted in the sickle cell anemia research Dr. Askari describes, where copper deficiency was induced after two years of zinc therapy. (*See* 2013 Askari Report 7).

myelopathy." *In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d at 1352 (alteration added)). Not much has changed. Plaintiffs' experts are still unable to "determine how much Fixodent must be used and 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.* As Dr. Askari testified, "we haven't defined the minimum level [of Fixodent] required to induce copper deficiency in any of the studies that I've reviewed." [44] (Jan. 2012 Askari Dep. Tr. 207:14–16 [ECF Nos. 2197-29, 30] (alteration added)). Dr. Lautenbach also testified there have been no epidemiologic assessments of a dose-response relationship between zinc-containing denture creams and the development of neurologic symptoms or disease. (*See* June 2013 Lautenbach Dep. Tr. 29:1–21).

The only available dose-response evidence is based on Wilson Disease research — which the Court has determined is not a reliable basis for inferring how much Fixodent is necessary to consistently induce a negative copper balance — and leaves considerable analytical gaps in Plaintiffs' general causation theory.

C. Other Experts

Plaintiffs' other general causation experts — Drs. Greenberg, Shuster, and Prohaska — do not provide the missing analytic epidemiological evidence, evidence of background risk of CDM, or evidence of a dose-response relationship.

Dr. Greenberg, a neurologist, primarily relies on textbooks and 142 peer-reviewed case

[44] Plaintiffs object to the relevance of Dr. Askari's 2012 deposition testimony as being "taken from the now out-dated *Jacoby* case." (Opp'n 89). In *Jacoby v. Rite Aid Corp., et al.*, No. 1508 EDA 2012, 2013 WL 6556743 (Pa. Super. Ct. Dec. 9, 2013) [ECF No. 2243-1], a related mass tort case involving claims that Fixodent caused CDM, the court affirmed the exclusion of Drs. Smith, Askari, and Lautenbach's opinions. Aside from the addition of the Fixodent Blockade Study and the cohort study, there are very few changes between Dr. Askari's *Jacoby* report (*see* [ECF No. 2224-4]) and his reports in this case; certainly none, in the Court's view, that change the relevance of this admission.

reports, 27 of which relate to denture cream use, to form his opinion that zinc in Fixodent can cause CDM. (*See* April 30, 2012 Expert Report of Steven A. Greenberg [ECF No. 2194-2]).[45] Dr. Shuster, a neurologist, did not submit an expert report, but Plaintiffs proffer her testimony that CDM is a generally-accepted diagnosis; and excess zinc, from zinc-containing denture creams such as Fixodent, can cause CDM. (*See* Opp'n 121). Dr. Shuster testified she did not know the amount of zinc contained in Fixodent and she believed "at one point there was an association with denture cream containing zinc or concern about that, especially in people that overused denture cream." (August 29, 2012 Deposition Testimony of Elizabeth M. Shuster 99:1–3; 39:8–11 [ECF No. 2197-43]). Particularly in light of this testimony, the Court does not find Dr. Shuster can provide the indispensible general causation evidence that has been missing in this case.

Dr. Prohaska, a biochemist and professor of biomedical sciences, was asked to render a report that provides an overview of the impact of copper status on the hematological system, in particular, hematological changes associated with copper deficiency and the impact of excess zinc on copper status and copper deficiency anemia. (*See* April 30, 2012 Expert Report of Joseph Prohaska ("Prohaska Report") 3 [ECF No. 2194-5]). Dr. Prohaska was not asked to render an opinion on the impact of copper status on the neurological system or whether zinc-containing denture adhesives can cause neurological disease. (*See* September 25, 2012 Deposition of Joseph Prohaska 106:5–10; 108:18–22; 110:6–9 [ECF No. 2194-13]). Dr. Prohaska testified he is not offering an opinion on the amount of zinc that must be ingested, or the duration of ingestion, to cause a negative copper balance (*see id.* 123:1–7); he is not offering

[45] Dr. Greenberg also prepared two rebuttal expert reports. (*See* August 30, 2012 Rebuttal Expert Report of Steven A. Greenberg [ECF No. 2194-3]; November 21, 2012 Rebuttal Expert Report of Steven A. Greenberg [ECF No. 2197-10]).

an opinion on the amount of zinc from denture adhesives that must be ingested, or the duration of ingestion, to cause a copper deficiency (*see id.* 123:8–17); nor is he offering an opinion on the bioavailability of zinc in zinc-containing denture creams (*see id.* 125:11–14). Additionally, other than case reports, Dr. Prohaska was not aware of any studies showing a connection between denture cream and copper deficiency. (*See id.* 27:9–28:16).

In light of the Court's determination that Plaintiffs have not presented sufficient or reliable evidence that Fixodent can cause copper deficiency myelopathy, the Court does not address the proffered testimony of Plaintiffs' non-causation experts, Drs. Cranor, Wogalter, or Raffa.

IV. CONCLUSION

On a record very similar to the one currently before the Court — where Plaintiffs had no analytic epidemiological evidence, no evidence of background risk of disease, and no knowledge of dose-response — the Eleventh Circuit affirmed the Court's *Chapman Daubert* Order finding Plaintiffs had not shown the zinc in Fixodent can cause CDM. *See Chapman*, 766 F.3d at 1308. After a thorough review of the law, the parties' briefing, and more evidence than is reflected in this Order, the Court again finds Plaintiffs have not presented sufficient proof of general causation using the indispensable primary methodologies identified by the Eleventh Circuit. *See id.* In light of this, the Court does not address the specific reliability of Dr. Lautenbach's Naranjo Scale analysis of the case reports or Dr. Smith's "weight-of-the-evidence" opinion, as such secondary methods of proving general causation are insufficient, have the potential to mislead a jury, and are thus inadmissible. *See id.*

As previously noted, "Plaintiffs have put forth a superficially appealing hypothesis that prolonged use of very large amounts of Fixodent may cause copper deficiency." *In re Denture*

Cream Prods. Liab. Litig., 795 F. Supp. 2d at 1367. Yet "the law requires more than a general theme to support causation — it requires a scientifically reliable connection." *Hendrix v. Evenflo Co., Inc.*, 255 F.R.D. 568, 600 (N.D. Fla. 2009) (internal quotation marks and citation omitted). The Fixodent Blockade Study, the cohort study, and Plaintiffs' experts' analyses do not make that scientifically reliable connection. While promising on its face, the "new evidence since *Chapman*" relies on factually inaccurate data and unsupported assumptions, and generally lacks the sound scientific basis and intellectual rigor required by *Daubert*.[46] These experts' opinions also leave significant gaps in Plaintiffs' general causation theory. "To admit the plaintiffs' evidence, the Court would have to make several scientifically unsupported 'leaps of faith' in the causal chain. The *Daubert* rule requires more. . . . 'The courtroom is not the place for scientific guesswork, even the inspired sort. Law lags science; it does not lead it.'" *Rider*, 295 F.3d at 1202 (alteration added) (quoting *Rosen v. Ciba-Geiga Corp.*, 78 F.3d 316, 319 (7th Cir. 1996)).

For the foregoing reasons, it is

ORDERED AND ADJUDGED that Defendants, The Procter & Gamble Company, The Procter & Gamble Distributing LLC, and The Procter & Gamble Manufacturing Company's

[46] Several other courts encountering the same experts and evidence agree. *See Jacoby*, 2013 WL 6556743 (affirming summary judgment in light of the fact plaintiff failed to produce admissible evidence of causation based on opinions by Drs. Smith, Askari, Lautenbach, and Grainger); *In re: Denture Adhesive Cream Litig.*, No. 4534 (Pa. Ct. Com. Pl. Phil. Cty. Feb. 10, 2014) (excluding opinions of Drs. Lautenbach, Askari, Smith, Greenberg, Cranor, Grainger, Prohaska, and Shuster; and finding the Fixodent Blockade Study and Dr. Lautenbach's cohort study unreliable as "nothing more than a blatant, litigation driven, attempt to remediate the analytical deficiencies identified in *Jacoby*") [ECF No. 2247-1]; *Adams v. The Procter & Gamble Distrib., LLC, et al.*, Case No. A1204223, 2014 WL 340129 (Ohio Ct. Com. Pl. Hamilton Cty. Jan. 22, 2014) (excluding the opinions of Drs. Askari, Grainger, Greenberg, Lautenbach and Smith given the scientific unreliability of the experts' opinions, and finding little evidentiary value in the Fixodent Blockade Study or Dr. Lautenbach's cohort study) [ECF No. 2246-1].

Motion to Exclude the Opinions of Plaintiffs' General Causation Experts [ECF No. 2197] is **GRANTED** in part.

DONE AND ORDERED in Miami, Florida, this 28th day of January, 2015.

CECILIA M. ALTONAGA
UNITED STATES DISTRICT JUDGE

cc: counsel of record