UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

IN RE: ZANTAC (RANITIDINE) PRODUCTS LIABILITY LITIGATION

MDL NO. 2924
20-MD-2924

JUDGE ROBIN L. ROSENBERG
MAGISTRATE JUDGE BRUCE E. REINHART

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OMNIBUS ORDER ON ALL PENDING *DAUBERT* MOTIONS AND DEFENDANTS' SUMMARY JUDGMENT MOTION

Table of Contents

I. Introduction 3
II. Factual and Procedural Background 7
A. Factual Background 8
B. Procedural Background 10
1. Creation of this MDL 10
2. Plaintiffs' Master Complaints 11
3. Discovery 14
4. Designated Cancers 14
C. Present Procedural Posture 15
1. Expert Reports 15
2. *Daubert* and Summary Judgment Briefing 18
III. Applicable Legal Standards 20
A. Admissibility of Expert Opinions 20
1. Qualification 21
2. Reliability 21
3. Helpfulness 23
B. General Causation 24
1. Definition of General Causation 24
2. General Causation Inquiry in this MDL 25
IV. Framing the General Causation Question in this MDL 29
V. Amount of NDMA in Ranitidine 35
A. Plaintiffs' Internal Testing for NDMA in Ranitidine 39
1. Dr. Najafi and Emery Pharma's Testing 39

AUTHENTICATED U.S. GOVERNMENT INFORMATION GPO

2. Experts Relying on Dr. Najafi and Emery Pharma's Testing 121
3. Final Ruling on Plaintiffs' Internal Testing 124
B. External Testing for Endogenous Formation of NDMA 124
1. *In Vivo* Studies 126
2. *In Vitro* Studies..... 145
C. Conclusion on the Amount of NDMA in Ranitidine 158
VI. Primary Evidence of General Causation 159
A. Epidemiology 161
1. Summary of Epidemiological Concepts..... 161
2. Summary of Parties' Arguments 168
3. Defendants' Generalized Challenges to Plaintiffs' Epidemiology Experts 169
4. Defendants' Specific Challenges to Plaintiffs' Epidemiology Experts 227
5. Final Ruling on Epidemiology Motion 298
B. Dose-Response Relationship 299
1. Dr. Salmon's Dose-Response Relationship and Threshold Dose Opinions..... 302
2. Remaining Experts' Dose-Response Relationship Opinions 309
3. Drs. Panigrahy, Michaels, McTiernan, and Moorman's Threshold Dose Opinions.... 313
C. Background Risk..... 319
D. Conclusion on Plaintiffs' Primary Evidence..... 321
VII. Secondary Evidence of General Causation 322
A. Animal Studies..... 322
1. Species and Dose Extrapolation..... 323
2. Cancer Diagnosis Extrapolation..... 330
B. FDA's Regulatory Risk Assessments 333
1. Parties' Arguments 333
2. Analysis..... 334
C. Conclusion on Plaintiffs' Secondary Evidence and Overall *Daubert* Conclusions..... 336
VIII. Summary Judgment 336
Appendix..... 338

I. Introduction

This multidistrict litigation ("MDL") is about Zantac heartburn medication or, more particularly, the molecule marketed under the label name of Zantac: ranitidine. Ranitidine is no longer sold in the United States and many other parts of the world because, in the spring of 2020, the U.S. Food and Drug Administration requested that the manufacturers of ranitidine voluntarily recall their products and cease all future sales. All manufacturers complied. The voluntary recall of ranitidine is a logical starting point for the facts underlying this MDL, but it is not the best starting point.

The best starting point involves a private company known as Valisure. Valisure theorized that ranitidine has the potential to degrade into a carcinogen known as NDMA. To evaluate this theory, Valisure tested batches of ranitidine in various conditions and found NDMA—lots of it. To put the Valisure test results into proper context, the FDA's self-determined daily limit for NDMA in a drug is 96 nanograms, or 96 ng. Valisure's tests found NDMA in ranitidine in excess of 3,000,000 ng.

To achieve a test result of 3,000,000 ng, however, Valisure had to heat the ranitidine to a temperature well above the 98 degrees Fahrenheit found in the human body; Valisure used a temperature of 266 degrees Fahrenheit. When Valisure tested ranitidine with a temperature of 98 degrees Fahrenheit, Valisure detected no NDMA.

Valisure's testing, however, extended beyond just temperature-based tests. Using the human body's base temperature, Valisure tested ranitidine's reaction with salt in an artificial stomach. Once ranitidine was mixed with salt, Valisure detected NDMA in excess of 300,000 ng. The amount of salt Valisure used, however, is worth noting. According to a Plaintiffs' expert in this MDL, the amount of salt Valisure used to generate 300,000 ng of NDMA was so great that it

was close to the level where, upon consumption, the salt intake would cause death. When Valisure tested ranitidine with salt concentrations more closely approximating what a human could safely ingest, Valisure detected no NDMA.

Valisure presented its findings to the FDA. The FDA did not immediately act on Valisure's information, however, for at least two reasons. First, the FDA concluded that the laboratory equipment that Valisure used to test for NDMA actually *created* NDMA. In other words, Valisure's laboratory equipment created the very substance for which it was testing. Second, the FDA wanted to conduct its own tests using laboratory equipment that did not create NDMA. Using its own laboratory equipment, the FDA tested ranitidine pills from several different manufacturers. Some of the ranitidine pills tested showed no NDMA or almost no NDMA. Others showed NDMA, but the NDMA was below the FDA's limit of 96 ng. Some ranitidine pills did show NDMA above 96 ng, but even the highest-tested pill showed NDMA at a tiny fraction of the level reported by Valisure.

Why then did the FDA initiate a voluntary recall of ranitidine? Although the FDA's tests revealed NDMA levels far below Valisure's, and although many of the FDA's tests showed NDMA levels that were acceptable, the fact remained that some of the FDA's tests showed ranitidine samples that eclipsed the 96 ng daily limit. Based upon the potential of some ranitidine pills to eclipse the 96 ng limit, the FDA initiated its voluntary recall of ranitidine.

Two key facts are important to an understanding of how the FDA's prior actions interplay with this case. First, one must consider what risk, if any, is posed by eclipsing the FDA's daily limit of 96 ng of NDMA. Second, one must consider the state of the science when this MDL was initiated. As for the FDA's daily limit, 96 ng per day (a nanogram is a billionth of a gram) is a conservative, protective limit. According to the FDA, one could expect to consume this much

NDMA from eating a meal of grilled or smoked meats, yet those foods are lawful to sell. Also, according to the FDA, if one were to consume 96 ng of NDMA every day, for 70 years in succession, the risk of cancer would be 1 in 100,000, or .001%.

As for the state of the science when this MDL was initiated, the first of the Plaintiffs' lawsuits were filed simultaneously with the Valisure petition to the FDA. Those lawsuits—and the first master complaint filed in this MDL—relied heavily upon Valisure's science. For example, the first master complaint in this MDL referred to Valisure's 266-degree heat as "modest" and the salt levels used by Valisure as "biologically relevant." Additionally, the Plaintiffs initially highlighted and relied upon a study overseen by Stanford University, which reported NDMA levels in ranitidine in excess of 47,000 ng.

Consistent with the FDA's findings as to the lack of validity of Valisure's laboratory equipment, the Plaintiffs ultimately elected not to rely upon Valisure's test results to prove their case. Relatedly, the Stanford University study was retracted by the study authors since, like Valisure, the Stanford laboratory equipment had created NDMA as part of the testing process. Much of the ranitidine-based science that *predated* this MDL, then, no longer furthered the Plaintiffs' case. As for ranitidine-based science that developed during the *pendency* of this MDL, that science also did not assist the Plaintiffs.

By way of example, the FDA commissioned a human clinical trial to determine whether ranitidine degrades into NDMA in the human body. That trial was completed in the summer of 2021 (a year after the voluntary recall and initiation of this MDL) and was conducted by FDA scientists. The FDA scientists concluded that they had found no evidence that ranitidine degrades into NDMA, even when the subjects in the study ate a diet rich with salt. Additionally, many epidemiological studies that focused on ranitidine were initiated and completed in 2020 and 2021,

after the voluntary recall. None of the ranitidine-focused epidemiological studies concluded that ranitidine causes cancer, and most of the studies concluded that there was not even an association (a far lesser standard than causation) between ranitidine and cancer.

In light of this evidence, the Plaintiffs elected to prove their case through two avenues. First, the Plaintiffs retained a chemist to test ranitidine for NDMA. Second, the Plaintiffs retained epidemiologists who based their opinions, not on the conclusions of any ranitidine-based study author, but instead (for the most part) upon the raw data found in studies that analyzed NDMA-rich food and NDMA-rich air.

The chemist that the Plaintiffs retained to test ranitidine for NDMA used laboratory equipment that differed from the laboratory equipment used by the FDA. Using his equipment, he found NDMA levels in ranitidine far, far higher than those found by any governmental body in the world.[1] For the reasons outlined in this Order, the methods used by the Plaintiffs' chemist were unreliable and resembled (in many respects) the testing conducted by Valisure. As the Court's ruling reflects, the only reliable testing of ranitidine puts the average amount of NDMA in ranitidine at roughly equivalent or slightly higher than the FDA's daily limit which, as discussed, equates to an infinitesimal, unprovable risk of cancer.

As for the Plaintiffs' reliance on studies of NDMA-rich foods and NDMA-rich air, those studies focused on the consumption of processed meats and the inhalation of fumes in rubber factories. Processed meats contain other carcinogens besides NDMA, and people struggle to accurately remember what they have eaten the prior day, let alone what they have eaten throughout the entire course of their lifetime. And the inhalation of rubber factory fumes (which also contain

[1] Before being retained as an expert, the Plaintiffs' chemist found NDMA in ranitidine at roughly the same level as the FDA; after being retained as an expert, his NDMA test results increased by more than an order of magnitude.

many carcinogens in addition to NDMA) is too far removed from the ingestion of ranitidine to be reliably applied in this MDL.

Thus, at first blush it may appear surprising that, notwithstanding the FDA's voluntary recall of ranitidine, the Court grants the Defendants' *Daubert* motions in full and strikes the Plaintiffs' experts. Once the Court's ruling is viewed in conjunction with the totality of the evidence on ranitidine, however, the Court's ruling is somewhat unremarkable. A common refrain in *Daubert* jurisprudence is that "law lags science," because the courtroom is not the appropriate forum for new scientific methodologies and theories to be tested; laboratories and published journals are the appropriate forum.

Here, there is no scientist outside this litigation who concluded ranitidine causes cancer, and the Plaintiffs' scientists within this litigation systemically utilized unreliable methodologies with a lack of documentation on how experiments were conducted, a lack of substantiation for analytical leaps, a lack of statistically significant data, and a lack of internally consistent, objective, science-based standards for the evenhanded evaluation of data. This Order is over 300 pages because the Court has endeavored to carefully explain each reason why the Plaintiffs' experts have utilized unreliable methodologies to reach their conclusions.

II. Factual and Procedural Background

In this section, the Court contextualizes the Order. First, the Court describes the history of ranitidine in the United States. The facts in this section are undisputed.[2] For ease of reference,

[2] This section is not a statement of undisputed material facts. The Defendants' motion for summary judgment is premised upon the Court granting their *Daubert* motions and, as a result, the Plaintiffs lacking admissible expert testimony on general causation. DE 5697 at 8. In this way, the motion for summary judgment is not premised upon particular facts. Facts that affect the outcome of the *Daubert* motions are discussed at length in the analyses of those motions.

the Court cites the Plaintiffs' filings, expert reports, and other materials.[3] Next, the Court describes the history of this case. And, last, the Court details the procedural posture of this case.

A. Factual Background

Ranitidine, the focus of this MDL, is a histamine-2 receptor blocker ("H2-blocker"). SAMPIC ¶ 48. Cimetidine, commonly known as Tagamet, famotidine, commonly known as Pepcid, and nizatidine, commonly known as Axid, are also H2-blockers. *Id.* H2-blockers decrease the amount of acid produced in the lining of the stomach. *Id.* Because of this property, H2-blockers treat heartburn and many other gastro-intestinal disorders, including duodenal ulcers, gastroesophageal reflux disease ("GERD"), and esophagitis. *Id.* ¶ 55; McTiernan Report at 258.[4] Proton pump inhibitors ("PPIs") also treat these conditions, but they typically treat more severe cases of them. Moorman Report at 211.

Ranitidine has been sold domestically for more than 35 years. GlaxoSmithKline first developed and patented Zantac, the brand-name of ranitidine. SAMPIC ¶ 50. In 1983, the FDA approved the sale of prescription Zantac. *Id.* ¶ 240. Then, in 1993, GSK entered a joint venture with Warner-Lambert to develop an over-the-counter ("OTC") form of Zantac, which the FDA approved in various forms in 1995. *Id.* ¶ 56. The joint venture between GSK and Warner-Lambert ended in 1998. *Id.* ¶ 57. Moving forward, Warner-Lambert controlled the sale of OTC Zantac in the United States, *id.*, and GSK controlled the sale of prescription Zantac, *id.* ¶ 59. In 2000, Pfizer acquired Warner-Lambert, along with the right to control the sale of OTC Zantac in the United

[3] The Plaintiffs have set forth their factual allegations in three "master" complaints: the Second Amended Master Personal Injury Complaint ("SAMPIC"); the Second Consolidated Amended Consumer Economic Loss Class Action Complaint ("SAELC"); and the Amended Consolidated Medical Monitoring Class Action Complaint ("AMMC") (collectively, the "Master Complaints"). DE 3883–84, 3887. Unless otherwise noted, all citations will be made to the redacted versions of the Master Complaints. All page number references to docket entries (i.e., citations beginning with "DE") herein are to the page numbers generated by CM/ECF in the header of each document.

[4] The Court simplified and abbreviated the titles of many filings. All page number references to filings cited by their titles herein, rather than by their docket entries, are to the page numbers that appear within the documents, not the page numbers generated by CM/ECF in the header of each document.

States. *Id.* ¶¶ 58-59. In 2006, Pfizer transferred this right to Boehringer Ingelheim Pharmaceuticals. *Id.* ¶ 62. In 2017, Boehringer Ingelheim ultimately sold the right to Sanofi. *Id.* ¶ 66.

Over time, Zantac became the first prescription drug to reach $1 billion in sales. *Id.* ¶ 53. In 2018, it was one of the top 50 most commonly prescribed drugs in the United States. Chris R. Cardwell et al., *Exposure to Ranitidine and Risk of Bladder Cancer: A Nested Case-Control Study*, Am. J. Gastroenterology, Aug. 2021, at 1, 2 (citation omitted). Naturally, when the patents on prescription and OTC Zantac expired, numerous generic drug manufacturers began producing generic ranitidine in prescription and OTC forms. DE 2760 ¶¶ 260-62.

After ranitidine had been on the market for 35 years, on September 9, 2019, Valisure LLC and ValisureRX LLC (together, "Valisure"), a pharmacy and testing laboratory, filed a Citizen Petition, calling for the recall of ranitidine because it found that ranitidine contained high levels of NDMA. SAMPIC ¶ 121. NDMA is an N-nitrosamine impurity. *See id.* ¶ 124. The FDA considers NDMA to be a carcinogenic impurity, *id.* at 78, the U.S. Environmental Protection Agency and the International Agency for Research on Cancer ("IARC") consider NDMA to be a probable human carcinogen, *id.* ¶ 74, and the U.S. Department of Health and Human Services considers NDMA to be a reasonably anticipated human carcinogen, *id.* ¶ 77. Studies have also shown that NDMA increases the risk of cancer in humans and animals. *Id.* ¶¶ 101-20. As a result of findings like these, the FDA had set an acceptable daily intake ("ADI") limit for NDMA at 96 nanograms, *id.* ¶ 101, and, in its Citizen Petition, Valisure claimed that it found levels of NDMA in ranitidine that exceeded this ADI limit by up to 3,000,000 nanograms, *id.* ¶ 168.

The FDA then tested ranitidine on its own to determine whether to recall it. On November 1, 2019, the FDA announced that it had found levels of NDMA that exceeded its ADI limit in

some ranitidine products. *Id.* ¶ 132; FDA, *Laboratory Analysis of Ranitidine and Nizatidine Products* (Nov. 1, 2019). Accordingly, the FDA recommended that drug manufacturers recall ranitidine products with NDMA levels above the ADI limit, SAMPIC ¶ 132, and several did, *id.* at 134. Five months later, on April 1, 2020, the FDA requested the voluntary withdrawal of all ranitidine from the market, *id.* ¶ 137, and the manufacturers complied.

B. Procedural Background

1. Creation of this MDL

When Valisure filed its Citizen Petition, and even before the FDA requested the withdrawal of all ranitidine from the market, plaintiffs around the country began filing lawsuits related to ranitidine. On February 6, 2020, the United States Judicial Panel on Multidistrict Litigation created this MDL pursuant to 28 U.S.C. § 1407 for all pretrial purposes and ordered federal lawsuits for personal injury and economic damages from the purchase or use of ranitidine to be transferred to this Court. DE 1.

The Court appointed leadership for both the plaintiffs and the defendants to manage the MDL. On the Plaintiffs' side, the Court appointed interim leadership teams,[5] then solicited and received applications from interested counsel for the formal leadership team, interviewed all sixty-two applicants, and appointed Plaintiffs' Leadership from among the applicants. DE 685. On the Defendants' side, the Court appointed an interim leadership team,[6] then solicited applications for the formal leadership team, and appointed Defendants' Leadership, after the Defendants notified the Court that they had reached a consensus as to its composition and structure. DE 708; DE 731;

[5] The Court appointed the Initial Census Team and the Practices and Procedures Team in Pretrial Order # 4. DE 68. In addition, the Court appointed the April Deliverables Team in Pretrial Order # 16 to prepare for the Initial Conference in this MDL. DE 557 at 7.
[6] The Court appointed the defense interim leadership team in Pretrial Order # 10. DE 409.

DE 747.[7] As part of their MDL management, Plaintiffs' and Defendants' Leadership by joint agreement proposed creating a Census Registry of potential unfiled claims. DE 547 at 1-2. The Registry was intended to enable the Court and the parties to readily understand the nature of the unfiled claims that are a part of this MDL. At the parties' request, the Court entered Pretrial Order # 15 memorializing their agreement. *See generally* DE 547.

Since the creation of the MDL, more than 2,450 plaintiffs have filed lawsuits or had them transferred to the United States District Court for the Southern District of Florida. Additionally, approximately one hundred fifty thousand potential claimants have registered their claims in the Registry. Plaintiffs and potential claimants have filed cases or registered claims, respectively, against the many entities, named as Defendants, that designed, manufactured, marketed, distributed, labeled, packaged, handled, stored, or sold ranitidine, alleging that their ranitidine use caused many different types of cancer.

2. Plaintiffs' Master Complaints

As this case progressed toward *Daubert*, its present procedural posture, the Plaintiffs filed three rounds of Master Complaints. On June 22, 2020, the Plaintiffs filed their first round of Master Complaints, suing defendants by category: Brand-Name Manufacturer Defendants, Generic Manufacturer Defendants (together, the "Manufacturer Defendants"), Distributor Defendants, Retailer Defendants, and Repackager Defendants. DE 887-89. The Brand-Name Manufacturer Defendants are GSK, Boehringer Ingelheim Pharmaceuticals, Chattem, Inc., Pfizer, and Sanofi, the companies that at some time controlled the sale of prescription and OTC Zantac. The Generic Manufacturer Defendants are seventy-one companies that produced generic ranitidine after the patents on prescription and OTC Zantac expired. The Distributor Defendants are four

[7] In Pretrial Order # 14, the Court authorized the interim leadership teams to continue to work on behalf of the parties until the Court selected the permanent leadership teams. DE 430.

pharmaceutical companies that sold ranitidine to retailers. The Retailer Defendants are thirty-six companies that sold ranitidine directly to consumers. And the Repackager Defendants are sixty-seven companies that repackaged or relabeled ranitidine and then sold the ranitidine under their own name.

In the first round of Master Complaints, the Plaintiffs pursued federal and state claims under the laws of all 50 U.S. states, Puerto Rico, and the District of Columbia. *See generally* DE 889. They claimed that all Defendants were liable in strict liability or negligence for failure to warn consumers of the dangers of ranitidine, failure to exercise reasonable care in supplying ranitidine to consumers, breach of warranty, and deceptive trade practices. DE 887 ¶¶ 453-72, 500-17, 542-61, 574-636. The Plaintiffs alleged that the Manufacturer and Repackager Defendants were liable in strict liability or negligence for ranitidine's design defects, negligent manufacturing, and misrepresentations in its labeling. *Id.* ¶¶ 473-49, 518-30, 531-41, 562-73. And they alleged that the Brand-Name Manufacturer Defendants were liable for Racketeer Influenced and Corrupt Organizations Act ("RICO") violations for defrauding consumers. DE 888 ¶¶ 749-93.[8]

The Defendants filed motions to dismiss the first round of Master Complaints. DE 1580, 1582-85, 1588, 1630, 2037, 2040, 2044-45. They argued that the Plaintiffs lacked Article III standing, failed to allege a cognizable injury, some of the Plaintiffs' claims were pre-empted, and the claims were impermissible shotgun pleadings. DE 2515 at 10-13; DE 2512 at 6; DE 2513 at 8. On December 31, 2020, in a series of orders, the Court found that the Plaintiffs' state-law claims against the Distributor and Retailer Defendants and the design defect and failure to warn claims against the Generic Manufacturer and Repackager Defendants were pre-empted. DE 2513 at 8; DE

[8] This list of claims is illustrative, not comprehensive. For context, the Plaintiffs' Consolidated Consumer Class Complaint contained 314 counts against the Defendants. DE 888.

2512 at 7. Additionally, the Court found that the Master Complaints were shotgun pleadings and granted the Plaintiffs leave to amend. DE 2515 at 13-14.

Thereafter, the Plaintiffs amended and filed their second round of Master Complaints, which specified the state law invoked for each claim and which corrected the Plaintiffs' shotgun pleading deficiencies. DE 2759, 2832-1, 2835. The Defendants filed motions to dismiss. DE 3105, 3107-09, 3111-16. The Distributor and Retailer Defendants argued that the Plaintiffs' negligence claims against them were implausibly pled. DE 3716 at 6. And the Manufacturer Defendants argued that the Plaintiffs' failure to warn claims and claims premised upon the sale of OTC ranitidine were pre-empted. DE 3715 at 8. On June 30, 2021, in another series of orders, the Court dismissed all claims in the Master Complaints against the Distributor, Retailer, and Generic Manufacturer Defendants, and the RICO claims against the Brand-Name Manufacturer Defendants with prejudice. DE 3715-16, 3718. The Court dismissed other claims without prejudice, granting the Plaintiffs leave to amend. DE 3719-20.

Ultimately, the Plaintiffs filed their third round of Master Complaints, amending their medical monitoring claims and providing greater clarity on the alleged facts supporting those claims. DE 3883-84, 3887. The Defendants again filed motions to dismiss. DE 4106-07. On October 6, 2021, the Court denied the motions to dismiss, DE 4487-88, and the Defendants filed their final answers, DE 4553-54, 4556-61, 4582-83. As a result, after three rounds of Master Complaints, related motions to dismiss, and orders resolving those motions, only claims against the Brand-Name Manufacturer Defendants (in this Order, the "Defendants") remained in the Master Complaints. The claims that remained are that the Defendants are liable for failing to warn consumers of the dangers of ranitidine through proper precautions and expiration dates, failing to test ranitidine for NDMA, negligently packaging and storing ranitidine, unjustly enriching

themselves, defrauding consumers, and tortiously causing the Plaintiffs to require medical monitoring. SAMPIC ¶¶ 264-2294; SAELC; AMMC. Significantly, the lynchpin of all of these claims is the proposition that ranitidine causes cancer.

3. Discovery

The parties stipulated and the Court ordered that the parties begin conducting discovery on June 15, 2020. DE 875 at 3. The parties agreed to conduct discovery on general causation and discovery of other facts simultaneously with staggered deadlines. DE 3200 at 1. To ensure discovery was timely, the Court set deadlines for production of custodial and non-custodial documents. *Id.* The Defendants for the most part met their production deadlines, while contending with delays caused by Covid-19 restrictions. Overall, discovery on general causation was to conclude by August 2, 2021. *Id.* The Plaintiffs asked for an extension for discovery on general causation to December 20, 2021, which the Court granted, and then for another extension for thirty-five days to January 24, 2022, which the Court also granted. DE 3619; DE 4657.

4. Designated Cancers

The parties stipulated to and the Court ordered Plaintiffs' Leadership to disclose the types of cancers for which they would provide expert reports. DE 875. On January 8, 2021, Plaintiffs' Leadership notified the Court of their intention to provide expert reports to prove that ranitidine causes bladder, breast, colorectal/intestinal, esophageal, gastric, kidney, liver, lung, pancreatic, and prostate cancers. DE 2533. On November 17, 2021, Plaintiffs' Leadership notified the Court that they no longer intended to provide general causation expert reports for breast and kidney cancers, narrowing their list from ten to eight cancers. DE 4676. On January 25, 2022, Plaintiffs' Leadership notified the Court that they no longer intended to provide general causation expert

reports for colorectal/intestinal, prostate, and lung cancers, narrowing their list from eight to five cancers. DE 5147.

Consequently, in their final disclosure, Plaintiffs' Leadership notified the Court of their intention to provide expert reports to prove that ranitidine causes bladder, esophageal, gastric, liver, and pancreatic cancers (the "Designated Cancers"), as opposed to all other cancers ("Non-Designated Cancers"). The Defendants do not address Non-Designated Cancers in their *Daubert* motions, so individual cases in which Plaintiffs allege their ranitidine use caused their Non-Designated Cancers remain pending at this time and are not the subject of this Order.

C. Present Procedural Posture

In the present procedural posture, Plaintiffs' Leadership seeks to prove that ranitidine causes the Designated Cancers. To do this, the Plaintiffs selected general causation experts, who prepared expert reports opining that ranitidine causes cancer. In response, the Defendants filed *Daubert* motions seeking to exclude all of the general causation experts for lacking reliable methodologies. The Court has carefully reviewed the Plaintiffs' expert reports, depositions of their experts, and much briefing to rule on the Defendants' motions. This next section lists the Plaintiffs' general causation experts, their opinions, and summaries of the briefing under consideration.

1. Expert Reports

The Plaintiffs selected the following general causation experts: Jennifer Le, Pharm.D., M.A.S., B.C.P.S.-I.D., F.I.D.S.A., F.C.C.P., F.C.S.H.P.; Michael Marletta, Ph.D.; Anne McTiernan, M.D., Ph.D.; Ronald L. Melnick, Ph.D.; Paul J. Michaels, M.D.; Patricia G. Moorman, M.S.P.H., Ph.D.; Ramin Najafi, Ph.D.; Charles Davis, Ph.D.; Dipak Panigrahy, M.D.; and Andrew Gale Salmon, M.A., D.Phil., C.Chem., M.R.S.C.

Dr. Le is a pharmacist. Dr. Le opines that ranitidine causes cancer based on published studies on "pharmacokinetics-pharmacodynamics, toxicology, and epidemiology of ranitidine and NDMA." Le Report at 8.

Dr. Marletta is a chemist and molecular biologist. Dr. Marletta opines that NDMA forms endogenously from ranitidine and that NDMA causes cancer based on his review of the relevant published literature. Marletta Report at 3-4.

Dr. McTiernan is an epidemiologist. Dr. McTiernan opines that to a "reasonable degree of medical and scientific certainty, use of ranitidine can cause cancer," based on her review of epidemiologic evidence. McTiernan Report at 15-16.

Dr. Melnick is a toxicologist. Dr. Melnick opines that NDMA is carcinogenic to humans based upon his review of the relevant published literature and other reports prepared for this litigation. Melnick Report at 7-9.

Dr. Michaels is a pathologist. Dr. Michaels opines that there is "substantial evidence . . . that treatment with ranitidine in doses and regimens that were directed by the product manufacturers can cause the development of cancers arising within the liver, stomach, esophagus, pancreas, and urinary bladder." Michaels Report at 3.

Dr. Moorman is an epidemiologist. Dr. Moorman opines that "ranitidine causes cancer in humans, and specifically it causes bladder, liver, pancreatic, esophageal, and stomach cancer." Moorman Report at 6. She stated that "to a reasonable degree of scientific certainty . . . the scientific community generally recognizes the toxicity and carcinogenicity of NDMA and specifically that it is likely a cause of human cancer" based on her review of epidemiologic evidence. *Id.* at 34.

Dr. Najafi is a chemist. Dr. Najafi investigated the presence and creation of NDMA in ranitidine. Najafi Report at 4. Dr. Najafi opines that ranitidine transforms into NDMA based on his own testing and review of published studies. *Id.* at 5-6.

Dr. Davis is a statistician. Dr. Davis opines on two data sets created by Dr. Najafi. Davis Report at 2. He found statistically significant differences in baseline NDMA-levels in ranitidine based on its form, storage, and status, opining that there seemed to be "increases in the NDMA level due to the number of cycles of shade, sun, and shower and due to the number of weeks for each zone." *Id.* at 6-7.

Dr. Panigrahy is a pathologist. Dr. Panigrahy opines that ranitidine exposure causes cancer based on his review of animal and human studies. Panigrahy Report at 9-13.

Dr. Salmon is a toxicologist. Dr. Salmon opines that ranitidine transforms into NDMA and causes cancer based on his review of human, dietary, occupational, and animal studies. Salmon Report at 7-8.

The parties prepared their expert reports pursuant to Pretrial Orders # 30 and # 65, which set forth the schedules for exchanging expert reports and deposing expert witnesses. DE 4660. The parties submitted to the Court the expert reports as they were prepared and the deposition transcripts as the transcripts were prepared during the spring of 2022. The parties also provided the Court with the scientific studies that their experts relied upon for their reports. In this way, the Court reviewed the general causation evidence on a rolling basis. Since that time, the parties have filed all of the reports and depositions on the master MDL docket and certified to the Court that the record is complete. DE 6057-59.[9]

[9] The Plaintiffs moved the Court to submit supplemental general causation expert reports to address a recent study: Chun-Hsiang Wang et al., *Pharmacoepidemiological Research on N-Nitrosodimethylamine-Contaminated Ranitidine Use and Long-Term Cancer Risk: A Population-Based Longitudinal Cohort Study*, Int'l J. Env't Rsch. & Pub. Health,

2. *Daubert* and Summary Judgment Briefing

The parties filed their briefing pursuant to Pretrial Order # 77, which set forth the *Daubert* and summary judgment briefing schedules. DE 5579. All of the briefing is listed in the appendix attached to this Order.

The Court considered the Brand Defendants' Roadmap Brief in Support of Their Motions to Exclude Plaintiffs' General Causation Experts and for Summary Judgment, DE 6030; Brand Defendants' Motion to Exclude Plaintiffs' General Causation Experts' Opinions Related to Epidemiology and Incorporated Memorandum of Law, DE 5736; Brand Defendants' Motion to Exclude Opinions and Testimony of Plaintiffs' Experts, Ramin Najafi, Ph.D., Charles Davis, Ph.D. and Other Experts who Rely on Their Opinions, DE 5732; and Brand Defendants' Motion to Exclude Remaining Expert Opinions Relating to General Causation and Incorporated Memorandum of Law, DE 5735.

In Brand Defendants' Roadmap Brief in Support of Their Motions to Exclude Plaintiffs' General Causation Experts and for Summary Judgment, the Defendants first outline the following three motions. Then the Defendants argue that, since the following three motions prove that the Plaintiffs do not have admissible expert testimony on general causation, the Court should grant summary judgment for the Defendants. DE 5697 at 2, 7.

In Brand Defendants' Motion to Exclude Plaintiffs' General Causation Experts' Opinions Related to Epidemiology and Incorporated Memorandum of Law (the "Epidemiology Motion"),

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Sept. 30, 2022, at 1. DE 6041. On October 5, 2022, the Defendants responded to the Plaintiffs' Expedited Motion, indicating that the Plaintiffs and Defendants had reached a tentative agreement, and filed a stipulation memorializing their ongoing negotiations. DE 6046; DE 6047. The Court granted in part the Plaintiffs' Expedited Motion. DE 6056. All supplemental expert reports and related depositions were reviewed by the Court on a rolling basis between October and November 2022 and later filed on the docket. DE 6061; DE 6071.

the Defendants argue that the Court should exclude the Plaintiffs' general causation experts because they lack reliable methodologies. DE 5699 at 5.

In Brand Defendants' Motion to Exclude Opinions and Testimony of Plaintiffs' Experts, Ramin Najafi, Ph.D., Charles Davis, Ph.D. and Other Experts who Rely on Their Opinions (the "Najafi Motion"), the Defendants argue that Dr. Najafi does not reliably measure the amount of NDMA found in ranitidine. Accordingly, the Defendants move to strike Dr. Najafi, and they argue that the expert opinions of others formed in reliance upon Dr. Najafi's data are unreliable.

In Brand Defendants' Motion to Exclude Remaining Expert Opinions Relating to General Causation and Incorporated Memorandum of Law (the "Secondary Evidence Motion"), the Defendants argue that several of the expert opinions based on secondary methodologies, including *in vitro* and animal studies, are unreliable and, therefore, inadmissible.

In light of this record, the Plaintiffs requested, without opposition from the Defendants, that the Court hold the *Daubert* hearing on the Defendants' motions without the parties' experts in attendance. The Court agreed and held two days of *Daubert* hearings on Defendants' motions on September 21 and 22, 2022. The Court has carefully considered the Defendants' *Daubert* motions, DE 5696; DE 5697; DE 5698; DE 5699; DE 5732; DE 5733; DE 5734; DE 5735; DE 5736, the Plaintiffs' responses, DE 5911; DE 5913; DE 5914; DE 5915, the Defendants' replies, DE 5956; DE 5957; DE 5958; DE 5960; DE 6005; DE 6029; DE 6030; DE 6032, the arguments made during oral argument, and the record. The parties have certified that the record the Court has used to analyze the motions is complete. DE 6057; DE 6058; DE 6059; DE 6095; DE 6102. For the reasons carefully detailed in this lengthy Order, the Court grants the Defendants' *Daubert* motions.

III. Applicable Legal Standards

A. Admissibility of Expert Opinions

The admissibility of expert testimony is governed by Federal Rule of Evidence 702, which 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.

Under Rule 702 and *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), expert testimony is admissible only if it is both reliable and relevant. *Rink v. Cheminova, Inc.*, 400 F.3d 1286, 1291 (11th Cir. 2005). Expert testimony is admissible, *i.e.* reliable and relevant, under Rule 702 if "(1) the expert is qualified to testify regarding the subject of the testimony; (2) the expert's methodology is sufficiently reliable as determined by the sort of inquiry mandated in *Daubert*; and (3) the expert's testimony will assist the trier of fact in understanding the evidence or determining a fact at issue." *Chapman v. Procter & Gamble Distrib., LLC*, 766 F.3d 1296, 1304 (11th Cir. 2014) (internal quotation marks and citation omitted). These criteria are known as "qualification, reliability, and helpfulness." *United States v. Frazier*, 387 F.3d 1244, 1260 (11th Cir. 2004).

Trial courts must act as "gatekeepers" to ensure that expert opinions meet the standards for admissibility and that "speculative and unreliable opinions do not reach the jury." *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1237 (11th Cir. 2005). The proponent of expert testimony

bears the burden of establishing qualification, reliability, and helpfulness by a preponderance of the evidence. *Hendrix ex rel. G.P. v. Evenflo Co., Inc*. (*Hendrix II*), 609 F.3d 1183, 1194 (11th Cir. 2010). Although there is overlap, courts and litigants alike "must take care not to conflate" these criteria. *See Frazier*, 387 F.3d at 1260.

1. Qualification

An expert must be qualified to testify to meet the first *Daubert* requirement. An expert may be qualified based on "knowledge, skill, experience, training, or education." Fed. R. Evid. 702; *Frazier*, 387 F.3d at 1261. The standard for qualification is not stringent, and an expert need only be minimally qualified in his or her field. *See Hendrix v. Evenflo Co.*, 255 F.R.D. 568, 578 (N.D. Fla. 2009), *aff'd sub nom. Hendrix II*, 609 F.3d 1183 (11th Cir. 2010). Qualification "is assessed in reference to the matter to which the expert seeks to testify—*i.e.*, 'to the task at hand.'" *Moore v. Intuitive Surgical, Inc.*, 995 F.3d 839, 854 (11th Cir. 2021) (quoting *Daubert*, 509 U.S. at 597). "It is for that reason that expertise in one field does not qualify a witness to testify about others." *Id.* (internal quotation marks and citations omitted).

2. Reliability

An expert's methodology must be sufficiently reliable to meet the second *Daubert* requirement. A court must assess "whether the reasoning or methodology underlying the [expert] testimony is scientifically valid and . . . whether that reasoning or methodology properly can be applied to the facts in issue." *Chapman*, 766 F.3d at 1306 (internal quotation marks and citation omitted). The court "must determine whether the evidence is genuinely scientific, as distinct from being unscientific speculation by a genuine scientist." *Id.* (internal quotation marks and citation omitted); *see also McClain*, 401 F.3d at 1244 (explaining that an "expert's assurances that he has utilized generally accepted scientific methodology are insufficient" and that a court must do more

than simply take "the expert's word for it" (alteration, internal quotation marks, and citation omitted)).

In *Daubert*, the Supreme Court identified four factors to guide assessment of an expert's methodology: (1) whether the expert's methodology has been tested or is capable of being tested; (2) whether the theory or technique used by the expert has been subjected to peer review and publication; (3) whether there is a known or potential error rate of the methodology; and (4) whether the technique has been generally accepted in the relevant scientific community. *Chapman*, 766 F.3d at 1305 (quoting *United Fire & Cas. Co. v. Whirlpool Corp.*, 704 F.3d 1338, 1341 (11th Cir. 2013) (citing *Daubert*, 509 U.S. at 593-94)). These factors are meant to help, but they are not a definitive or exhaustive checklist. *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 151 (1999). All four factors may not even apply each time the reliability of expert testimony is challenged. *Id*. at 150.

A court may consider the additional factors of whether the opinion was created for the purpose of litigation and whether the expert stands to benefit financially from his or her testimony. *See Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1321 (11th Cir. 1999); *Lust By & Through Lust v. Merrell Dow Pharms., Inc.*, 89 F.3d 594, 597 (9th Cir. 1996) (noting that an expert was a plaintiff's witness in a different case at the time he published his article and presuming he was "influenced by a litigation-driven financial incentive"). Additionally, an opinion is not reliable when there is "too great an analytical leap between the [supporting] data and the opinion proffered." *Hendrix II*, 609 F.3d at 1194 (citing *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)). An "expert opinion is inadmissible when the only connection between the conclusion and the existing data is the expert's own assertions." *McDowell v. Brown*, 392 F.3d 1283, 1300 (11th Cir. 2004); *c.f. Joiner*, 522 U.S. at 146 ("[N]othing 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 has "considerable leeway in deciding in a particular case how to go about determining whether particular expert testimony is reliable" and whether the factors "are reasonable measures of the reliability of expert testimony." *Kumho Tire Co.*, 526 U.S. at 152. But there are still limits on the court's discretion. The court's role is not to "make ultimate conclusions as to the persuasiveness of the proffered evidence." *Quiet Tech DC-8, Inc. v. Hurel-Dubois UK Ltd.*, 326 F.3d 1333, 1341 (11th Cir. 2003). "Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." *Daubert*, 509 U.S. at 596.

3. Helpfulness

An expert's testimony must be helpful to meet the third *Daubert* requirement. To be helpful, expert testimony must fit the facts of the case. *McDowell*, 392 F.3d at 1298-99; *Allison*, 184 F.3d at 1312. To do so, it must "logically advance[] a material aspect of the case" and "assist the trier of fact." *McDowell*, 392 F.3d at 1299 (internal quotation marks and citation omitted). "Fit is not always obvious, and scientific validity for one purpose is not necessarily scientific validity for other, unrelated purposes." *Daubert*, 509 U.S. at 591 (internal quotation marks and citation omitted).

Just as an opinion is unreliable if it is based upon an analytical leap that is too great, there not a fit when "a large analytical leap must be made between the facts and the opinion." *McDowell*, 392 F.3d at 1298-99 (citing *Joiner*, 522 U.S. at 146).[10] An "expert opinion is inadmissible when

[10] Because courts consider "analytical leaps" under both the reliability and helpfulness prongs of *Daubert*, this Court considers analytical leaps under both prongs as well.

the only connection between the conclusion and the existing data is the expert's own assertions." *Id.* at 1300.

B. General Causation

The Court sets forth below a definition of general causation. After the Court's definition, the Court explains why a general causation inquiry is necessary in this MDL.

1. Definition of General Causation

As will be discussed in greater detail in the following section, the Eleventh Circuit has stated that toxic tort cases come in two broad categories. "The first category consists of cases in which the medical community generally recognizes the toxicity of the substance at issue to cause the injury plaintiff alleges." *Chapman*, 766 F.3d at 1303 (alterations, internal quotation marks, and citations omitted). The second category consists of cases "where the medical community generally does not recognize the substance in question as being toxic and having caused plaintiff's alleged injury." *Id.* The second category of cases require "a two-part *Daubert* analysis," as the court must assess the reliability of the expert opinions on both general and specific causation. *Id*.

"General causation refers to the general issue of whether a substance has the potential to cause the plaintiff's injury." *Id.* at 1306 (internal quotation marks and citation omitted). "General causation is concerned with whether an agent increases the incidence of disease in a group and not whether the agent caused any given individual's disease." *McClain*, 401 F.3d at 1239 (internal quotation marks and citation omitted). In contrast, specific causation focuses on questions such as "was plaintiff exposed to the toxin, was plaintiff exposed to enough of the toxin to cause the alleged injury, and did the toxin in fact cause the injury?" *Id.*

Experts may rely upon different types of evidence to prove or disprove general causation, including as bases for an inference of general causation, including epidemiological studies,

toxicological studies (dose-response relationship), and physiological-mechanism evidence. *In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d 1345, 1351 (S.F. Fla. 2011). As discussed in further detail below, these types of evidence are not all afforded the same weight.

2. General Causation Inquiry in this MDL

Before the Court analyzes the Defendants' *Daubert* motions, the Court addresses an argument the Plaintiffs make that, were the Court persuaded, would mean the Court would not undertake a general causation review of the Plaintiffs' evidence. The Plaintiffs' argument concerns the case of *McClain v. Metabolife International, Inc.*, 401 F.3d 1233 (11th Cir. 2005).

In *McClain*, the plaintiffs took an herbal weight-loss supplement. 401 F.3d at 1236. Alleging that the supplement caused them serious medical problems, the plaintiffs took the case to trial and obtained a jury verdict in their favor. *Id.* The defendant appealed, arguing that the trial court's decision to admit the plaintiffs' experts' testimony on causation was error. *Id.* The Eleventh Circuit agreed with the defendant and reversed the jury's verdict. *Id.*

In describing why the trial court erred, the Eleventh Circuit divided toxic tort cases into two categories. *Id.* First, the Eleventh Circuit identified cases where the "medical community generally recognizes the toxicity of the drug or chemical at issue," and second, the Eleventh Circuit identified "those cases in which the medical community does not generally recognize the agent as both toxic and causing the injury the plaintiff alleges." *Id.* at 1239. The Eleventh Circuit provided concrete examples of cases involving the first category, such as asbestos and cigarette smoke. *Id.* In cases involving such well-known toxins, the Eleventh Circuit clarified that the trial court "need not undertake an extensive *Daubert* analysis on the general toxicity question when the medical community recognizes that the agent causes the type of harm a plaintiff alleges." *Id.* Instead, the

first category of cases focuses on individual plaintiff causation, while the second category—toxins that are not generally known—focuses on both general causation and individual causation. *Id.*

The Plaintiffs do not contend that the drug at issue in this case, ranitidine, is generally recognized by the scientific community as a carcinogen capable of causing cancer. What the Plaintiffs argue is that a component of ranitidine—the NDMA formed from ranitidine degradation—is well known to be a carcinogen and, as a result, ranitidine falls into the first category of cases described in *McClain*. Because ranitidine falls into the first category, the Plaintiffs argue, this Court need not undertake any general causation inquiry at all—the Defendants' *Daubert* motions should be summarily denied pursuant to *McClain*.

Subsequent to *McClain*, courts in this Circuit have considered the question of how *components* of drugs should be treated under *McClain*. In *In re Denture Cream Products Liability Litigation*, the plaintiffs alleged that a denture adhesive cream, Fixodent, caused them to develop myelopathy, a condition caused by a copper deficiency in the body. 795 F. Supp. 2d at 1347-48. Arguing that their copper deficiency was caused by excessive zinc in Fixodent and that the toxicity of excessive zinc was well established in the scientific community, the plaintiffs argued that their case fell into the first category of *McClain*. *Id.* at 1351 n.9. Because the plaintiffs' theory of the case turned on the toxicity of zinc, the plaintiffs argued that zinc—not Fixodent—was the agent at issue for *McClain* purposes and that they need only show that Fixodent contained zinc. *Id.* Conversely, the defendant argued that the agent at issue for *McClain* purposes was Fixodent, not zinc, even if Fixodent contained zinc. *Id.*

The trial court agreed with the defendant for various reasons, substantiating its conclusion with the following logical chain of the plaintiffs' theory of the case:

(1) Fixodent contains zinc.

> (2) The zinc in Fixodent can be absorbed by the body.
>
> (3) Absorption of enough zinc from any source can induce a negative copper balance.
>
> **(4) One can ingest enough zinc from Fixodent to place the body in a negative copper balance.**
>
> (5) Over time a zinc-induced negative copper balance can lead to a copper deficiency.
>
> (6) A prolonged copper deficiency in humans can cause a myelopathy.
>
> (7) Therefore, Fixodent can cause a myelopathy.

Id. at 1357-58 (emphasis added). The trial court noted that the Plaintiffs' *McClain* argument failed on item (4) above because there was no general consensus in the scientific community that Fixodent consumption could result in sufficient zinc intake to cause the plaintiffs' alleged injury. *Id.* at 1358. Additionally, the trial court compared Fixodent, containing zinc, to the examples given by the Eleventh Circuit for category one cases—asbestos and cigarette smoke—and found that Fixodent containing zinc did "not have the same widespread acceptance by the medical community as the Eleventh Circuit's examples." *Id.* at 1350 n.8. The trial court found the plaintiffs lacked reliable evidence on general causation and excluded the plaintiffs' experts. *Id.* at 1367.

The plaintiffs appealed. *Chapman*, 766 F.3d at 1296. The Eleventh Circuit found that the trial court had properly treated Fixodent, which contained zinc, as a *McClain* category two case, not a category one case. *Id.* at 1303-04 ("[T]he district court properly determined that Fixodent, containing zinc, was in *McClain* category two [which is where] . . . . the medical community generally does not recognize the substance in question as being toxic.").

At oral argument in this MDL,[11] the Plaintiffs argued three different grounds as to why the Fixodent district and circuit court cases are distinguishable. First, the Plaintiffs argued: "Unlike

[11] The Plaintiffs did not cite or discuss the Fixodent cases in their briefing.

zinc in Fixodent . . . NDMA has no beneficial practical purpose. It is exclusively used to induce cancerous tumors in laboratory experiments." Defendants' Sept. 21 *Daubert* Hearing Tr. at 63-64. Second, the Plaintiffs stated: "In those cases they were referring to a zinc calcium compound which was in Fixodent and not zinc acetate, which is what the science that they were looking at pertained to." *Id.* at 72-73. Third, the Plaintiffs contended: "In those cases, there was no, zero, supportive epidemiology regarding the substance or the toxin at issue, there was none." *Id.* at 72. The Court finds these grounds to be unpersuasive.

The Court has reviewed the Fixodent cases in detail. The beneficial uses of zinc had no bearing on the courts' application of *McClain* to the case, and, although the differences between the zinc in Fixodent and the zinc in various studies did feature into the reasoning of the trial court, that was but one reason among many that the plaintiffs did not meet their *Daubert* evidentiary burden; the Fixodent courts found that *McClain* category one did not apply because the plaintiffs had to show that Fixodent—not zinc, generally—could cause the injury at issue. Third and finally, for all of the reasons set forth in Section VI(A), *infra*, the plaintiffs in this MDL lack primary evidence of epidemiology.

The Court finds that this case is a *McClain* category two case that requires a general causation inquiry for four reasons. First, the facts in this MDL are not distinguishable from the facts in the published, binding Fixodent decision by the Eleventh Circuit. Second, even if the Fixodent appellate case is distinguishable and is therefore not binding, the reasoning in the Fixodent cases is persuasive—the Plaintiffs must show that ranitidine consumption can result in sufficient NDMA ingestion to cause their alleged injuries. Third, the Plaintiffs' position leads to untenable results. NDMA is a ubiquitous substance found in trace amounts in air, water, and food. Taken to its logical conclusion, the Plaintiffs' *McClain* reasoning would mean that the scientific

community generally accepts the proposition that air, water, vegetables, and many meats cause cancer—so much so that no plaintiff in the Eleventh Circuit need produce evidence for those propositions. Fourth, the Court's detailed analysis based on the totality of the evidence, set forth throughout the entirety of this Order, shows that the Plaintiffs have no reliable primary evidence on general causation. This lack of reliable evidence underscores the necessity for undertaking such an inquiry in the first place. Stated simply, ranitidine is not a cigarette. The Court will therefore turn to its analysis of the Defendants' *Daubert* motions and the framing of the general causation question in this MDL.

IV. Framing the General Causation Question in this MDL

The Defendants contextualize their challenge to the Plaintiffs' epidemiological experts with the following facts:

> For 35 years, tens of millions of patients relied on ranitidine, also known as Zantac, to treat heartburn, stomach ulcers, gastroesophageal reflux disease ("GERD"), erosive esophagitis, and other conditions. In that time, ranitidine was studied extensively and repeatedly found to be safe and effective. No regulatory agency or scientific body ever concluded that ranitidine was a risk factor for or cause of cancer.
>
> . . . .
>
> Since 2019, researchers from 17 medical institutions have published 11 peer-reviewed studies, analyzing data from nearly seven million patients, to assess whether real-world use of ranitidine, including any NDMA ranitidine may contain, causes cancer. None of these studies, nor any regulatory body or medical association, has concluded that ranitidine causes cancer. To the contrary, over the past three years of research, independent investigators and regulatory agencies consistently concluded that there was "no evidence" of any increased risk. They found "no demonstrable association" between ranitidine and cancer types, "no association between ranitidine and overall or specific cancer risk" and "no evidence of a causal association between ranitidine therapy and the development of cancer in patients." They also concluded that their results should "alleviate concerns of patients exposed to ranitidine," and that ranitidine patients should find the results "reassuring." Summarizing the totality of peer-reviewed evidence, FDA concluded "no consistent signals emerged, and studies with comparison to active controls found no association between ranitidine and overall or specific cancer risk."

DE 5699 at 8-9 (footnotes omitted). Based upon these facts, the Defendants frame the general causation question for this MDL as follows:

> **Does the scientific evidence reliably demonstrate that use of therapeutic doses of Zantac (ranitidine) can cause any of the Designated Cancers?**

Defendants' Sept. 21 *Daubert* Hearing Tr. at 7. In their Response, the Plaintiffs approach the general causation question from a different angle:

> The question for this Court is straightforward: can any expert witness opine that the NDMA in ranitidine can cause cancer? The question is not whether NDMA in ranitidine actually did cause a Plaintiff's cancer—that is a specific causation question. Instead, the relevant inquiry is categorical, and asks whether any Plaintiff, whatever the facts of his cancer or usage, could possibly have cancer caused by NDMA in ranitidine. Plaintiffs' experts concluded the answer to that question is "yes." This Court must decide if that affirmative opinion was based on such a flawed methodology that a jury cannot even hear it, let alone consider it.

DE 5915 at 8. Based upon their reasoning quoted above, the Plaintiffs frame the general causation question as follows:

> **Whether a reasonable jury could conclude that the NDMA in ranitidine is capable of causing human cancer at the highest realistic exposure level any plaintiff may have experienced?**

See Defendants' Sept. 21 *Daubert* Hearing Tr. at 192.

The Defendants' and the Plaintiffs' framing of the general causation question differs in four respects. First, only the Defendants' framing of the question takes into account the distinction between Designated and Non-Designated Cancers. Second, the Defendants refer to the *Daubert* standard, "[d]oes the scientific evidence reliably demonstrate," while the Plaintiffs refer to the summary judgment standard, "whether a reasonable jury could conclude." Third, the Defendants limit their focus to ranitidine while the Plaintiffs refer to "the NDMA in ranitidine." Fourth, the Defendants refer to "therapeutic doses" while the Plaintiffs refer to "the highest realistic exposure level any plaintiff may have experienced."

The Court will address each of these differences in turn, however, it is worth noting that the parties' competing general causation questions do not alter the Court's decision. For the reasons outlined in this Order, even if the Court were to frame the general causation question exactly as the Plaintiffs have requested, based on the totality of the evidence, the Court would grant the Defendants' *Daubert* motions in full.

First, as to Non-Designated Cancers and Designated Cancers, the Court concludes that the best framing of the general causation question takes this distinction into account. The Court does not decide in this Order whether the Plaintiffs have established general causation for Non-Designated Cancers.

Second, the Plaintiffs' reliance on the summary judgment standard and the Defendants' reliance on the *Daubert* standard for purposes of framing the general causation question are reconcilable. It is self-evident that the Plaintiffs must satisfy *Daubert*. They must have, as the Defendants put it, reliable scientific evidence. As the Defendants have also moved for summary judgment, it is equally evident that the Plaintiffs must satisfy the summary judgment standard—they must have evidence of general causation that a reasonable jury could rely upon. Of course, a reasonable jury may rely upon scientific expert testimony that flows from a reliable scientific methodology. The Court therefore concludes that the best framing of the general causation question references the *Daubert* standard because it is *Daubert*—not the summary judgment standard—at the heart of the Court's inquiry in this Order.

Third, the Plaintiffs' reference to "NDMA in ranitidine" and the Defendants' omission of any reference to NDMA is a distinction without any meaningful difference. The product in this MDL is ranitidine. A jury would decide whether ranitidine caused any Plaintiff's cancer. The Plaintiffs' theory for *how* ranitidine causes cancer is, of course, that it degrades into NDMA. The

Court resolves the parties' dispute by framing the general causation question on the product the Plaintiffs consumed, ranitidine, in lieu of the mechanistic theory by which the Plaintiffs seek to prove their case, NDMA.

The last distinction between the parties' competing general causation questions, dose, comes the closest to being a distinction that matters, but is still ultimately unimportant. The Defendants focus on whether a lower, therapeutic dose could cause cancer.[12] The Plaintiffs focus on a very high dose—the most any Plaintiff could have "realistically" taken—and whether that dosage could cause cancer.

At this point in the Court's discussion, it is helpful to address *why* the Plaintiffs have premised their general causation question on the maximum dosage any Plaintiff could have "realistically" consumed. The reason is the concept of "threshold dose," or the dosage at which ranitidine consumption can cause cancer. The parties dispute whether the Plaintiffs must identify the threshold dose at which ranitidine consumption causes cancer. The Plaintiffs argue that they do not have to identify *how much* ranitidine consumption can cause cancer—the threshold—and may instead show that the highest dosage any Plaintiff could have realistically consumed could cause cancer. The Defendants argue that the Plaintiffs must identify the point at which ranitidine consumption becomes toxic—the threshold.

Thus, when the Defendants frame the general causation question at a *lower* dose, while the Plaintiffs frame the general causation question at the *highest possible* dose (which disregards the concept of threshold dose), the parties are embedding their legal dispute over threshold dose into the general causation question. Although the Court will address threshold dose at length in Section

[12] In a prior Order, the Court expressed its inability to locate a definition for a "therapeutic" dose level. DE 3720 at 30-31. Neither party has adequately defined or explained what a "therapeutic" dose is.

VI(B), *infra*, the Court sets forth in this section some case law on the issue to aid in framing the general causation question.

The Defendants' position on threshold dose is well grounded in binding, published, and analogous Eleventh Circuit case law. In *Chapman v. Proctor & Gamble Distributing, LLC*, the Eleventh Circuit noted that all substances have the potential to become toxic if exposure to it is high enough, but that the plaintiff had failed to produce evidence on "**how much** [product] must be used **for how long** to increase the risk."[13] 766 F.3d at 1307 (emphasis added). In *In re Deepwater Horizon Belo Cases*, No. 3:19-cv-963, 2020 WL 6689212 (Nov. 4, 2020), this Court noted that a general causation expert must "demonstrate the **levels** of **exposure** that are **hazardous** to human beings **generally**." *Id.* at *9 (emphasis added) (quoting *McClain*, 401 F.3d at 1241). In *In re Accutane Products Liability*, a trial court in this Circuit expressed the following: "Dose is critical to any evaluation of toxicity of a drug." 511 F. Supp. 2d 1288, 1293 (M.D. Fla. 2007).

The Plaintiffs' best argument on this issue is that they are not required to define a threshold dose with specificity. The Defendants do not contest that this is true, however, "a plaintiff must demonstrate 'the levels of exposure that are hazardous to human beings generally as well as the plaintiff's actual level of exposure.'" *McClain*, 401 F.3d at 1241 (quoting *Wright v. Willamette Indus., Inc.*, 91 F.3d 1105, 1106 (8th Cir. 1996)). The Defendants concede that a threshold range would satisfy Eleventh Circuit case law. *See* Defendants' Sept. 21 *Daubert* Hearing Tr. at 45 ("[S]ome numbers are required, that is what case law says, a range, an estimate, and they don't do it.").

The Court concludes that the Plaintiffs must identify a threshold dose range at which ranitidine can cause cancer for two reasons. *See infra* Section VI(B). First, the case law requires

[13] The Court discusses *Chapman* in detail in Section VI(A)(3)(b), *infra*, and the Court discusses why a threshold dose is a necessary part of an expert's reliable methodology in its discussion on dose-response in Section VI(B), *infra*.

that a plaintiff must identify a threshold dose, even if the dose is described only as a range. Second, the Plaintiffs minimize the importance of the concept of the *amount* of any potential risk from ranitidine consumption. The question of general causation is not satisfied simply because an infinitesimal risk of cancer is more than zero risk. Courts universally reject general causation theories based upon the idea that *any* amount of a carcinogen, no matter how small, is actionable because an infinitesimal risk can neither be proven nor disproven. Thus, since an actionable exposure threshold dose cannot, as a matter of law, be merely *anything*, that means it must be *something provable*.

There are two related but equally important questions at play here. First, when does a substance become toxic? *See McClain*, 401 F.3d at 1241. This is the question that the Defendants emphasize. But, after a threshold exposure is identified, there is a second inquiry—could any Plaintiff have consumed the threshold dose? *See id.* This is the question that the Plaintiffs emphasize by focusing on the highest dose any Plaintiff could have realistically consumed; if that dose was higher than the threshold dose, a specific causation inquiry becomes necessary.

In summary, both parties are correct. The Defendants are correct that the Plaintiffs must identify at least a range at which ranitidine consumption becomes toxic, which the Court addresses at length in Section VI(B), *infra*. Assuming that the Plaintiffs satisfy their evidentiary burden to identify the threshold range at which ranitidine consumption becomes toxic, the Plaintiffs are correct that if any Plaintiff could have realistically consumed the threshold dose the Court's inquiry would shift from general causation to specific causation.

As a result, the Court frames the general causation question as follows:

> **Does the scientific evidence reliably demonstrate that ranitidine is capable of causing a Designated Cancer at the highest realistic exposure level any plaintiff may have experienced?**

The general causation question has two parts. First, do the Plaintiffs have reliable scientific evidence "that ranitidine is capable of causing a Designated Cancer?" This inquiry focuses on the capacity of ranitidine to cause cancer. Second, what is the "highest realistic exposure level" a Plaintiff in this MDL may have experienced? This inquiry applies the theoretical potential of ranitidine to cause cancer to the facts and circumstances of this MDL. At the center of both inquiries is the amount of NDMA in ranitidine. The amount of NDMA in ranitidine is therefore an important issue in this MDL, and many of the Defendants' specific *Daubert* challenges touch upon this question in one way or another.

V. Amount of NDMA in Ranitidine

The Court has never been able to ascertain with clarity how much NDMA the Plaintiffs allege ranitidine contains. DE 3720 at 26 ("[T]he Court has conducted an extensive review of the [master complaints] in an effort to determine the amount of NDMA each ranitidine dose is alleged to contain. The Court has been able to locate four different sets of numbers, and each set has been referenced by the Plaintiffs in their various responses throughout the entirety of this MDL."). The Plaintiffs' Master Complaints contain allegations as low as 4 ng of NDMA per pill and as high as 3,000,000 ng per pill. *Id.* at 26-29. At Science Day, the Court inquired as to the specifics of the Plaintiffs' position on NDMA, but only learned that what "We are going to demonstrate is that [sic] taking one ranitidine pill has the same NDMA as several pounds of bacon." Dec. 2 Science Day Proceedings Tr. at 91.

The uncertainty on this issue has continued into the *Daubert* stage of these proceedings because the Plaintiffs' experts reference various NDMA testing results, even when the expert does not rely upon the data to form an opinion. For example, Dr. McTiernan references NDMA laboratory testing conducted by fellow expert Dr. Najafi, but she does not base her opinion on Dr.

Najafi's numbers. McTiernan Report at 14. Instead, Dr. McTiernan bases her opinion on test results from the FDA. *Id.* Additionally, the Plaintiffs reference test results upon which no expert relied. *See* DE 5915 at 16.[14] In an effort to distill down the data, the Court divides NDMA testing into four categories.

First, FDA tests showed a significant range of NDMA in ranitidine pills, from as low as 10 ng per pill to as high as 360 ng per pill. Salmon Report at 211-12. Even though the Plaintiffs' experts (at least for the most part) rely upon this data, the Court has been unable to locate the *average* amount of NDMA the FDA detected. The Court's best analysis of the data, however, is that the average amount of NDMA detected by the FDA, per 150 mg pill, was less than the FDA's daily limit for NDMA of 96 ng per pill. *See id.*[15]

Second, the Defendants' own internal testing showed a range of NDMA per pill, with a minimum amount of NDMA of 0 ng and a maximum amount of NDMA of 435 ng, per 150 mg pill. *Id.* at 212. Some of the Plaintiffs' experts rely upon this data to form an opinion. For example, Dr. Salmon uses the Defendants' internal testing and the FDA's testing, together, to compute an average amount of NDMA, per 150 mg pill, of 144 ng. *Id.*

Third, the Plaintiffs retained an expert, Dr. Najafi, for the express purpose of quantifying NDMA exposure from ranitidine production and distribution. Dr. Najafi's tests resulted in an average amount of NDMA per pill (approximately 1,000 ng) that far exceeded the results of FDA

[14] The Plaintiffs in their Response to the Defendants' Epidemiology Motion reference a GSK NDMA test, representing that the test stands for the proposition that ranitidine contains as much as 12,420 ng of NDMA per 300 mg ranitidine pill. Yet the Plaintiffs' citation corresponds to a 150 mg test, not a 300 mg test, to a test of manufacturing ingredients, not a finished ranitidine product, to a substance almost 5 years old, not something within the United States' expiration guidelines, and to an outlier datapoint approximately 50 times greater than the average of all of GSK's tests. *See* DE 5912-5 at 357-61. No expert relies upon the Plaintiffs' cited 12,420 ng number to compute an average amount of NDMA per ranitidine pill.

[15] The Court's best analysis of the data is based upon Dr. Salmon's conclusion that three of the ranitidine batches tested by the FDA had average NDMA values below 96 ng and one batch had an average value above 96 ng. Salmon Report at 212.

testing. Some of the Plaintiffs' experts rely upon Dr. Najafi's results in the formation of their expert opinions. *E.g., id.* at 223.

Fourth and finally, the Plaintiffs rely upon endogenous formation evidence for the proposition that whatever the amount of NDMA that was formed through production and distribution (such as the amount of NDMA detected by the FDA), additional NDMA is formed during digestion in the human stomach. The Plaintiffs utilize this evidence to argue that the amount of NDMA shown in the above-referenced tests is conservative, and the actual amount of NDMA from ranitidine consumption is higher.

The variance in the data on the amount of NDMA in ranitidine, together with how one estimates the danger flowing from that data, results in a large variance in the estimated potential risk of ranitidine consumption. At one end of the spectrum are the FDA's tests, showing a mean amount of NDMA per pill of less than 96 ng.[16] According to the FDA, 96 ng of NDMA would, if it were taken every day for 70 years, result in an infinitesimal, unobservable risk of cancer of .001%. *See infra* Section VII(B). This computation by the FDA stands in contrast to the risk of cancer as computed by the Plaintiffs' expert Dr. Salmon who, at the opposite end of the spectrum, uses the much higher NDMA testing results of Dr. Najafi. Using those numbers and using a different methodology than the FDA to compute risk, Dr. Salmon concludes that the cancer risk from ranitidine consumption is greater than a 50% increase, and that such risk may be generated from as little as 1.5 years of ranitidine use. Salmon Report at 221-23.

The Defendants do not challenge the reliability of the FDA's tests. Similarly, the Defendants do not challenge the reliability of their own tests. The Defendants *do* challenge the

[16] According to the Plaintiffs' expert Dr. Salmon, if the Defendants' tests are analyzed together with the FDA's tests, the median NDMA content, per 150 mg pill, is around 144 ng and is therefore slightly above the FDA's acceptable daily limit. Salmon Report at 212.

reliability of Dr. Najafi's tests, and they also challenge the Plaintiffs' evidence that NDMA can be formed endogenously during digestion.[17] Below, in Section V(A), the Court addresses the Defendants' *Daubert* challenges to Dr. Najafi's tests. In Section V(B), the Court addresses the Defendants' challenges to the Plaintiffs' endogenous formation evidence. In Section V(C), the Court sets forth its conclusion regarding the Plaintiffs' evidence on the amount of NDMA in ranitidine.

Before the Court turns to Section V(A), the Defendants' *Daubert* challenges to Dr. Najafi's tests, it is worth noting that Section V(A) corresponds to one of the Defendants' three *Daubert* motions; the Defendants devoted a fifty-page motion to Dr. Najafi's tests and experts that relied upon Dr. Najafi's tests. *See* DE 5698; DE 5732. Together with the necessary background information for the reader to understand Dr. Najafi's tests, Section V(A) is quite long, and it is quite detailed. The length and detail of Section V(A) and the Defendants' *Daubert* Motion is derived from the fact that Dr. Najafi conducted many kinds of tests on ranitidine. He tested ranitidine with various temperatures, with various amounts of salt, and with different kinds of foods. The Defendants challenge the reliability of all of the tests. The Court's analysis is therefore extensive because it must analyze the tests conducted by Dr. Najafi and the challenges to them. Ultimately, the Court concludes that Dr. Najafi used unreliable methodologies to conduct his tests and that Dr. Najafi's tests may not be used to answer the question of how much NDMA was in the Plaintiffs' ranitidine.

Section V(B), which addresses the Plaintiffs' endogenous formation evidence, is also quite lengthy. Like Section V(A) and Dr. Najafi's tests, the Defendants devoted almost an entire *Daubert* motion to the Plaintiffs' endogenous evidence. *See* DE 5696; DE 5735. Section V(B)'s

[17] The Defendants also challenge the reliability of Dr. Salmon's methodology wherein he uses NDMA data to estimate cancer risk. That challenge is addressed in Section VI(B), *infra*.

length is derived from the many different types of endogenous tests that the Plaintiffs' experts analyzed, such as laboratory tests on artificial human stomachs and human-based tests in the form of clinical trials. As with Dr. Najafi, the Plaintiffs' experts utilize unreliable methodologies to conclude that ranitidine degrades into NDMA inside of the human body.

A. Plaintiffs' Internal Testing for NDMA in Ranitidine

The Court explains in more detail below the specific arguments that the parties raise concerning Dr. Najafi's testing of ranitidine. Stated broadly, however, the Defendants contend that Dr. Najafi's expert opinions, which are based on testing that his laboratory conducted on ranitidine and ranitidine active pharmaceutical ingredient ("API"), are unreliable and unhelpful to this litigation. The Defendants assert that Dr. Davis' expert opinions are likewise unreliable and unhelpful because they are based exclusively on his statistical analysis of the results of Dr. Najafi's laboratory's tests. The Defendants' Najafi Motion does not challenge the qualifications of Dr. Najafi, Dr. Davis, or any other expert.

In Section V(A)(1), the Court examines Dr. Najafi's opinions and the testing that his laboratory conducted. Then the Court addresses Dr. Davis' opinions in Section V(A)(2)(a) and the opinions of Drs. Le, McTiernan, Moorman, Panigrahy, and Salmon who rely on Dr. Najafi's testing in Section V(A)(2)(b).

1. Dr. Najafi and Emery Pharma's Testing

Dr. Najafi has a Ph.D., M.S., and B.S. in organic chemistry. He is the founder of three companies: CP Lab Safety, NovaBay Pharmaceuticals, Inc., and Najafi Pharma Inc., dba Emery Pharma ("Emery Pharma" or "the laboratory"). The third of Dr. Najafi's companies, Emery Pharma, operates an FDA-registered and -inspected research laboratory located in Alameda, California. Dr. Najafi is the current CEO of Emery Pharma. *See generally* DE 5698-10 at 202-14

(Dr. Najafi's curriculum vitae). Emery Pharma is the laboratory that conducted the ranitidine and ranitidine API testing that is the subject of the Defendants' Najafi Motion at docket entry 5698 seeking to have Dr. Najafi's opinions stricken.

Before being retained to serve as an expert for the Plaintiffs in this litigation, Dr. Najafi signed a Citizen Petition on behalf of Emery Pharma and submitted it to the FDA on January 2, 2020. *See* DE 5698-45. That Citizen Petition explained that Emery Pharma had conducted testing on (1) ranitidine API that was stored at a temperature of 25 °C/77 °F for up to two weeks, and (2) ranitidine API and finished ranitidine products that were stored at a temperature of 70 °C/158 °F for up to two weeks. *Id.* at 3. The goal of this testing was to assess the potential for NDMA to accumulate in ranitidine and ranitidine API. *Id.*

The Citizen Petition reported that the ranitidine API stored at room temperature (25 °C/77 °F) showed "no significant increase in NDMA" and was "seemingly stable." *Id.* at 3, 6. Meanwhile, the ranitidine API stored at the higher temperature (70 °C/158 °F) progressively accumulated NDMA. The laboratory detected 18 ng of NDMA per 150 milligram ("mg") dose of ranitidine in that ranitidine API at day 0 and detected 142 ng of NDMA per 150 mg dose of ranitidine at day 12.[18] *Id.* at 3. As for finished ranitidine products, Emery Pharma tested four such products stored at 70 °C/158 °F. Emery Pharma Rule 30(b)(6) Dep. at 130-31. Although the laboratory tested four products, the Citizen Petition reported only on the one product, a Zantac Cool Mint product, that had accumulated the highest levels of NDMA over a two-week period. *Id.*; DE 5698-45 at 3. Emery Pharma reported that its testing of this Zantac Cool Mint product revealed that the level of NDMA increased from 19 ng per 150 mg dose of ranitidine at day 0 to

[18] Dr. Najafi frequently refers to a 150 mg dose because that was a common dosage of OTC ranitidine. *See, e.g.*, John P. Cunha, *Ranitidine*, RxList (June 7, 2021), https://www.rxlist.com/consumer_ranitidine_zantac/drugs-condition.htm. One mg is one thousandth of a gram. One ng is one billionth of a gram.

70 ng per 150 mg dose of ranitidine at day 14. DE 5698-45 at 3. The laboratory purchased the Zantac Cool Mint product OTC from a pharmacy. Emery Pharma Rule 30(b)(6) Tr. at 128.

Emery Pharma explained in its Citizen Petition that this testing indicated "that the ranitidine molecule may not be heat stable, and under elevated temperatures, generates significant amounts of [NDMA], a probable human carcinogen." DE 5698-45 at 2. According to the laboratory, these test results were concerning because ranitidine could be exposed to elevated temperatures both during commercial shipment and storage and once it had reached consumers. *Id.* at 3-4, 7-8. Emery Pharma further stated that "[t]he propensity for ranitidine to generate NDMA at 70°C suggests that such accumulation may be possible at lower temperatures, albeit at a slower rate." *Id.* at 7.

Emery Pharma made several requests to the FDA as a result of its testing. These requests included that ranitidine products be recalled and their sale suspended, that ranitidine be thoroughly investigated, that ranitidine products be dispensed only by prescription, that manufacturers and distributors be required to ship ranitidine products in temperature-controlled vehicles, and that the public be warned about ranitidine's instability when exposed to heat. *Id.* at 4-5. On April 1, 2020, three months after Emery Pharma had submitted the Citizen Petition, the FDA asked manufacturers to immediately withdraw all ranitidine products from the consumer market, advised consumers taking OTC ranitidine to stop using the products, and recommended that patients taking prescription ranitidine consult with their health care professionals about other treatment options.[19]

The Plaintiffs retained Dr. Najafi as an expert in January 2020. Najafi Dep. at 24. The Plaintiffs asked Dr. Najafi to "investigate the presence of [NDMA] in ranitidine [API] and

[19] *See* Press Release, FDA, FDA Requests Removal of All Ranitidine Products (Zantac) from the Market (Apr. 1, 2020), https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market.

Zantac/ranitidine finished drug products including analyzing samples of ranitidine API and Zantac/ranitidine finished drug product for the possible presence of NDMA." Najafi Report at 4. If NDMA were found, Dr. Najafi was to "conduct an investigation into its source, and identify the factors giving rise to its presence in API and Zantac/ranitidine finished drug product." *Id.* The Plaintiffs further asked Dr. Najafi to "investigate and test whether ranitidine can cause NDMA formation *in vivo*" and to "if possible, quantify the amount of potential exposure to NDMA from ranitidine drug products." *Id.*

To comply with the Plaintiffs' requests, Dr. Najafi directed Emery Pharma to conduct various tests on ranitidine products and ranitidine API. Given that ranitidine products had been withdrawn from the consumer market, the laboratory received much of the ranitidine and ranitidine API that it used for its testing from Defendants GSK, BI, Sanofi, and Patheon. According to Dr. Najafi, Emery Pharma's tests revealed up to thousands of nanograms of NDMA per 150 mg dose of ranitidine. *Id.* at 5. Also according to Dr. Najafi, subjecting ranitidine to heat and/or humidity causes significantly greater levels of NDMA to form within the ranitidine tablet. *Id.* Dr. Najafi concludes based on additional testing that, in addition to NDMA forming within ranitidine tablets themselves, ranitidine can cause "significant amounts" of NDMA to form endogenously (that is, within the human body) when the drug interacts with nitrite in food and gastric fluid in the human stomach. *Id.* at 5-6. Dr. Najafi opines that ranitidine is an unstable molecule that transforms into NDMA and that heat and humidity accelerate the rate of this transformation. *Id.* at 10. Dr. Najafi does not offer an opinion as to whether ranitidine causes cancer. *See generally* Najafi First Rebuttal Report; Najafi Dep. at 187 (providing confirmation from the Plaintiffs that Dr. Najafi is "not offering an opinion on general causation and doses that cause cancer").

Dr. Najafi discusses Emery's Pharma's testing, the test results, and his conclusions in a report dated January 24, 2022, and in two rebuttal reports dated March 28 and April 12, 2022. *See* Najafi Report; Najafi First Rebuttal Report; Najafi Second Rebuttal Report. He was deposed on May 26, 2022. *See generally* Najafi Dep. The Court addresses the Defendants' arguments challenge by challenge. First, the Court considers (a) how Emery Pharma validated its testing methods and (b) how Emery Pharma documented its testing methods. Next, the Court considers (c) Dr. Najafi's reliance on assistants and (d) Dr. Najafi's lack of peer review for his methodology. Finally, the Court considers Emery Pharma's (e) "baseline" testing, (f) "consumer experience" testing, (g) "simulated gastric fluid" testing, and (h) "miscellaneous" testing.

a. **Validation**

One issue in this litigation is the validity of the methods of chromatography, including chromatography integration, that Emery Pharma used during its ranitidine testing. Chromatography is a technique that is used to physically separate a substance, called the "analyte," into its molecular components so those components may be detected, identified, and quantified. *See generally* USP, *<621> Chromatography* (2018) [hereinafter *USP General Chapter <621>*]. A court evaluating the admissibility of expert testimony must assess whether the testimony is the product of reliable, scientifically valid principles and methods. *E.g.,* Fed. R. Evid. 702(c); *Chapman*, 766 F.3d at 1306. In a case involving scientific evidence, the trustworthiness of the evidence is based on scientific validity. *Daubert*, 509 U.S. at 590 n.9. "'Validity' refers to the ability of a test to measure what it is supposed to measure—its accuracy." *Reference Manual on Scientific Evidence* 71 (3d ed. 2011); *see also Daubert*, 509 U.S. at 590 n.9 (referring to "validity" in the sense of whether a "principle support[s] what it purports to show").

The United States Pharmacopeia ("USP") is an independent nonprofit organization that establishes drug standards in the United States and publishes best practices for drug testing.[20] The USP states that a "prerequisite" of an analytical procedure used to assess drug stability is that the procedure be "appropriately validated." USP, *<1010> Analytical Data—Interpretation and Treatment* 2-3 (2020) [hereinafter *USP General Chapter <1010>*]. "Validation of an analytical procedure is the process by which it is established, by laboratory studies, that the performance characteristics of the procedure meet the requirements for the intended analytical applications." USP, <1225> *Validation of Compendial Procedures* 1 (2021) [hereinafter *USP General Chapter <1225>*]. Simply stated, validation "is the process of demonstrating that an analytical procedure is suitable for its intended purpose." U.S. Dep't of Health & Hum. Servs., FDA, Ctr. for Drug Evaluation & Rsch., Ctr. for Biologics Evaluation & Rsch., *Analytical Procedures and Methods Validation for Drugs and Biologics: Guidance for Industry* 7 (2015) [hereinafter *Analytical Procedures and Methods Validation for Drugs and Biologics*].

The characteristics that are typically used to assess the validity of an analytical procedure are accuracy, precision, specificity, detection limit, quantitation limit, linearity, range, and robustness. *E.g., USP General Chapter <1225>*, *supra*, at 1-2. Several of these characteristics are relevant to the Court's evaluation of Emery Pharma's testing and of Dr. Najafi's opinions. Accuracy refers to "the closeness of test results obtained by [a] procedure to the true value." *Id.* at 2. Precision refers to "the degree of agreement among individual test results when [a] procedure is applied repeatedly to multiple samplings of a homogenous sample." *Id.*; *see also* FDA, Ctr. for Drug Evaluation & Rsch., *Reviewer Guidance: Validation of Chromatographic Methods* 1, 134 (1994) [hereinafter *Validation of Chromatographic Methods*] (describing precision as "the

[20] *See generally USP*, https://www.usp.org. The USP's drug standards carry the force of federal law. *See* 21 U.S.C. §§ 321(j), 351(b).

measure of how close the data values are to each other for a number of measurements under the same analytical conditions"). Specificity refers to the ability to unequivocally assess a substance at issue in the presence of other components that may be present, such as impurities. *USP General Chapter <1225>*, *supra*, at 3.

There are various methods of chromatography. *See generally USP General Chapter <621>*, *supra*. One such method is gas chromatography. During gas chromatography, heat is used to vaporize the analyte into its gaseous form. A flowing stream of a gas such as helium, nitrogen, or hydrogen carries that gaseous analyte into a column. *Id.* at 3-4. *See generally Validation of Chromatographic Methods*, *supra*. This carrier gas is called the "eluant." The step of chromatography during which the analyte is carried to the column is commonly called the "mobile phase" or "moving phase." *Validation of Chromatographic Methods*, *supra*, at 4. The column contains an adsorbent material such as alumina, silica, or carbon.[21] *USP General Chapter <621>*, *supra*, at 4. The analyte is pushed through the column during a step commonly called the "stationary phase." *Id.* As the analyte moves through the column, its components move at different speeds, and therefore are separated, due to physical differences in factors such as absorption, solubility, and molecular size. *Id.* at 4, 7-8. The components "elute" from (that is, exit) the column at different times due to the different speeds at which they are moved through the column. *Id.*

Because most substances require significant heat to become and remain vaporized, gas chromatography typically utilizes a high temperature. The FDA has stated that gas chromatography "is not suitable for testing ranitidine because heating the sample generates

[21] Adsorption is a process where the atoms or molecules from one substance adhere to the surface of a second substance, called the adsorbent. This process is distinguishable from absorption, where the atoms or molecules of a substance enter and are dissolved into a second substance.

NDMA."[22] That is, the testing method itself causes NDMA to form, so the method is not suitable to measure the level of NDMA that existed in the sample of ranitidine before the test was conducted.

Another type of chromatography is liquid chromatography. During liquid chromatography, a liquid solution (rather than heat) is used to dissolve the analyte. *Id.* at 4-5. For the mobile phase, a stream of a liquid (rather than gaseous) eluant transports the analyte to the column, and the analyte then moves through the column for the stationary phase to achieve separation. *Id.* Liquid chromatography does not necessitate the use of high temperatures such as those used during gas chromatography. Most separations take place at room temperature. *See, e.g.*, Press Release, FDA, FDA Updates and Press Announcements on NDMA in Zantac (Ranitidine) (Oct. 2, 2019), https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine. The FDA has validated two methods of liquid chromatography to measure the levels of NDMA in ranitidine and ranitidine API: liquid chromatography-high resolution mass spectrometry ("LC-HRMS") and liquid chromatography-tandem mass spectrometry ("LC-MS/MS").[23]

After separated components of an analyte elute from the column following either gas or liquid chromatography, the components pass through a detector such as a mass spectrometer. *USP General Chapter <621>*, *supra*, at 2-5. The output of the detector is plotted on a graph called a chromatogram. *Id.* at 5. A chromatogram consists of a series of peaks on a time axis, with the time

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[22] *See* Press Release, FDA, FDA Updates and Press Announcements on NDMA in Zantac (Ranitidine) (Oct. 2, 2019), https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine ("The higher temperatures generated very high levels of NDMA from ranitidine products because of the test procedure. . . . That method is not suitable for testing ranitidine because heating the sample generates NDMA.").

[23] *See generally* FDA, *Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) Method for the Determination of NDMA in Ranitidine Drug Substance and Drug Product* (2019), https://www.fda.gov/media/130801/download; FDA, *Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) Method for the Determination of NDMA in Ranitidine Drug Substance and Solid Dosage Drug Product* (2019), https://www.fda.gov/media/131868/download.

axis reflecting the time that it took the components to elute from the column. *Id.*; *Validation of Chromatographic Methods*, *supra*, at 1-2. A peak on a chromatogram represents a component that has been detected. *USP General Chapter <621>*, *supra*, at 6. The amount of area under a peak represents the quantity of the component that was present in the analyte. *Id.*

One method that may be used to check the accuracy of chromatography is an internal standard. An internal standard is a known quantity of a compound that is added to an analyte. John W. Dolan, *When Should an Internal Standard Be Used?*, 30 LCGC N. Am. 474 (2012), https://www.chromatographyonline.com/view/when-should-internal-standard-be-used-0. After chromatography separates the analyte, the quantity of the internal standard compound that is detected is compared to the known quantity of that compound that was added. *Id.* If only a portion of the known quantity added has been detected, that information can be used to calculate the ratio of the analyte components that are being detected. *Id.*; *see also* Najafi Dep. at 501 ("Let's say I add 20 nanogram [sic]. If during my testing I only detect 10, then my recovery is 50 percent, so the same thing will happen to the NDMA. So if I pick up . . . 500 nanograms in the pill, I should multiply it by two because of . . . what that standard is telling me.").

Integration refers to the identification of a peak on a chromatogram that corresponds to a particular component of the analyte and to the determination of the quantity of the component that the peak represents. Integration can be conducted automatically or manually. During automatic integration, a computer algorithm in processing software determines the peak, and the area of that peak, that represents a particular component. Strengths of automatic integration include that integration is performed consistently and that concerns about the integrity of the data are reduced. Mark E. Newton & R.D. McDowall, *Data Integrity in the GxP Chromatography Laboratory, Part III: Integration and Interpretation of Data*, 36 LCGC N. Am. 330 (2018),

https://www.chromatographyonline.com/view/data-integrity-gxp-chromatrography-laboratory-part-iii-integration-and-interpretation-data ("Consistency in peak processing is a strength in automatic integration, and one of many reasons for adopting it."); *id.* (explaining that "automation provides consistency from analyst to analyst and run to run"); *id.* ("Autointegration of all injection peaks is the expectation. Automatic integration reduces the data integrity risk to the organization, increases consistency in results, and significantly reduces the time to review chromatograms . . . .").

During manual integration, an analyst can override the computer software's integration and adjust the area under a peak by manually repositioning a peak's "baseline," that is, where the peak starts and stops. *See id.* A baseline may be manually repositioned to reduce the peak's area, which is called "peak skimming" or "peak shaving." *Id.*; Bob McDowall, LCGC N. Am., *Controlling Chromatographic Integration to Ensure Data Integrity* (2018). Or, the baseline may be manually repositioned to increase the peak area, a process called "peak enhancing" or "peak enhancement." Newton & McDowall, *supra*; McDowall, *supra*.

Manual integration is "a powerful data manipulation tool." McDowall, *supra*. "Leaving an audit trail of a large number of reintegrations produces the impression of 'playing' with the data to get a desired result." *Id.* (stating that peak skimming and peak enhancement "would be viewed as highly suspicious by a regulatory agency"); *see also* Newton & McDowall, *supra* (referring to peak skimming and peak enhancing as "bad integration practices used to falsify data" and stating that "[t]hese two practices must be eliminated in all regulated laboratories"). Frequent manual integration may be a sign of inadequate analyst training, equipment that needs servicing, or a flawed method. McDowall, *supra* (stating that "[i]deally, separation and detection conditions should be adjusted so that manual integration is not necessary"); *see also* Newton & McDowall,

supra (explaining that the need for manual integration should be reduced by "devoting sufficient resources to method development").

Having written, laboratory-wide standard operating procedures for integration "is critical to ensuring proper and defendable processing of data." McDowall, *supra* (explaining that the FDA requires an approved procedure for manual integration); *see also* Newton & McDowall, *supra* ("To succeed, a robust [standard operating procedure] for chromatographic integration is essential in today's environment."). Written standard operating procedures "must clearly define when and to what degree intervention in the automated integration system is allowed, and how it should be performed." McDowall, *supra*; *see also* Newton & McDowall, *supra* (advising laboratories that they may alleviate regulatory concerns if they "only perform manual integrations under conditions permitted in your firm's chromatography [standard operating procedures] or analytical procedures," and listing various topics that should be included in such procedures).

"In some cases, it may be best to disallow manual integration altogether." McDowall, *supra*. Where manual integration is allowed, "the number of times it can be performed should be limited," and "[a]ll integration attempts must be saved and available for review." *Id.*; *see also* Newton & McDowall, *supra* ("Audit trail reason codes entered by users must provide sufficient detail to permit an inspector to reconstruct the sequence and actions performed by laboratory personnel."); U.S. Dep't of Health & Hum. Servs., FDA, Ctr. for Drug Evaluation & Rsch., Ctr. for Veterinary Med., *Bioanalytical Method Validation: Guidance for Industry* 18 (2018) [hereinafter *Bioanalytical Method Validation*] ("The basis for changing or reprocessing data should be documented with sufficient detail, and the original record should be maintained."). The FDA has issued warnings to laboratories in instances where the agency discovered extensive

manipulation of data without explanation and without guiding standard operating procedures. *See, e.g.*, Newton & McDowall, *supra* (providing examples of FDA warning letters).

i. Parties' Arguments

The Defendants argue that Dr. Najafi has not demonstrated the validity of the method of chromatography Emery Pharma used to measure the NDMA content of ranitidine and ranitidine API. Emery Pharma used a method of chromatography—a method that the Defendants refer to as hydrophilic interaction chromatography ("HILIC")—that is "completely different" than the two methods of liquid chromatography the FDA has validated to measure the levels of NDMA in ranitidine. DE 5698 at 8-9, 18, 41; DE 5956 at 12. No scientist outside of Emery Pharma has used or validated HILIC for the specific purpose of measuring NDMA in ranitidine. DE 5698 at 8-9, 18, 41; DE 5956 at 12. The Defendants further argue that "many" of the integrations that Emery Pharma's analysts made when processing the results of their chromatography were manual, DE 5698 at 44, and that the laboratory has no standard operating procedures, parameters, or criteria for manual integration, *id.* at 18, 44; DE 5956 at 7-8.

The Plaintiffs respond that Emery Pharma used an FDA-validated method of chromatography and state-of-the-art instrumentation to measure the levels of NDMA in ranitidine and ranitidine API. DE 5914 at 7, 24-28. The laboratory validated its method of chromatography and used internal standards to confirm the validity of its method. *Id.* at 7, 25-27. The Plaintiffs also argue that it is a widely acceptable practice for laboratory analysts to manually integrate when processing the results of chromatography. *Id.* at 7.

ii. Analysis

The Court addresses Emery Pharma's methods of chromatography and chromatography integration.

Emery Pharma's Method of Chromatography

The Defendants contend that Emery Pharma used a "completely different" method of chromatography than any method that the FDA has validated for measuring NDMA in ranitidine. That argument is inaccurate because Emery Pharma used LC-MS/MS, and LC-MS/MS is one of the two methods of chromatography that the FDA has validated for testing ranitidine and ranitidine API. Najafi Report at App. A; FDA, *Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) Method for the Determination of NDMA in Ranitidine Drug Substance and Solid Dosage Drug Product* 1 (2019) [hereinafter FDA, *LC-MS/MS*], https://www.fda.gov/media/131868/download. Rather, it is the column (one of the instruments used during LC-MS/MS) that Emery Pharma used to conduct its chromatography that is different than the column that the FDA included as part of its validated LC-MS/MS procedure for measuring NDMA in ranitidine.

The Plaintiffs' argument that the column the laboratory used—a HILIC column—is simply a different subtype of column than what the FDA included in its validated procedure is also inaccurate. That argument is inaccurate because the column the FDA included in its validated procedure separates an analyte through what is called a reverse-phase mode of separation. *Id.* at 3. The HILIC column that Emery Pharma utilized, on the other hand, separates an analyte differently than a reverse-phase column. *E.g.,* Boguslaw Buszewski & Sylwia Noga, *Hydrophilic Interaction Liquid Chromatography (HILIC)—A Powerful Separation Technique*, 402 Analytical & Bioanalytical Chemistry 231, 231 (2011) ("Hydrophilic interaction liquid chromatography (HILIC) is an alternative high-performance liquid chromatography . . . mode for separating polar compounds."); Thermo Scientific, *HILIC Separations: A Practical Guide to HILIC Mechanisms, Method Development and Troubleshooting* 3 (2014) (referring to HILIC as "the opposite of

conventional reversed phase chromatography"). Dr. Najafi himself has acknowledged that a reverse-phase column and a HILIC column separate an analyte differently. *See* Najafi First Rebuttal Report at 9 (reporting that "HILIC was developed as an alternative to traditional reversed phase" and that Emery Pharma determined that a HILIC column provides "a better mode of separation for NDMA" than a reverse-phase column).

The difference between a reverse-phase mode of separation and a HILIC mode of separation has to do with how the components of an analyte move through the column during the stationary phase of chromatography. A HILIC column contains an absorbent material that retains polar molecules longer than does the absorbent material in a reverse-phase column, meaning that the polar molecules travel through the HILIC column more slowly and elute later.[24] Thermo Scientific, *supra*, at 3. A HILIC column ideally achieves better separation of an analyte that contains polar components. *Id.* (explaining that HILIC "is the most successful approach for the retention and separation of polar compounds"). To explain the distinction between reverse-phase columns and HILIC columns in the context of ranitidine, NDMA elutes before other components of ranitidine if a reverse-phase column is utilized for the chromatography. But because NDMA is a polar molecule, it is retained in the column longer and elutes after other components of ranitidine if a HILIC column is used. Defendants' Sept. 22 *Daubert* Hearing Tr. at 139-40.

Emery Pharma used a reverse-phase column for the chromatography that it conducted for the purpose of filing its Citizen Petition with the FDA. Najafi First Rebuttal Report at 9. For the studies that the laboratory conducted for this litigation, however, the laboratory switched to using a HILIC column for the majority of the studies.[25] Dr. Najafi has explained that Emery Pharma

[24] A polar molecule is one where different parts of the molecule have different electrical charges.
[25] Emery Pharma continued to utilize a reverse-phase column for the studies for this litigation that involved a liquid, such as studies using simulated gastric fluid ("SGF") and tests on injectable and syrup forms of ranitidine. Defendants'

made this change in instrumentation because the laboratory determined that a HILIC column would achieve better separation of ranitidine than would a reverse-phase column. *Id.* ("Emery Pharma . . . found that Hydrophilic Interaction Liquid Chromatography (HILIC) is a better mode of separation for NDMA when many different ranitidine products are considered."); *id.* ("Emery determined that the BEH Amide column offers better selectivity and separation for NDMA . . . as NDMA is a highly polar analyte, and HILIC was developed as an alternative to traditional reversed phase just for such analytes.").

The Court considers the *Daubert* factors as applied to Emery Pharma's use of a HILIC column to conduct chromatography with ranitidine and ranitidine API. The application of the *Daubert* factors demonstrates that the Plaintiffs have not carried their burden to show that Emery Pharma's use of a HILIC column is a reliable methodology for separating NDMA from ranitidine and ranitidine API.

First, based on the record, Emery Pharma is the only laboratory to have used a HILIC column when conducting chromatography with ranitidine. The two chromatography procedures that the FDA has validated for measuring NDMA in ranitidine and ranitidine API both use a reverse-phase column to achieve separation. *See* FDA, *Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) Method for the Determination of NDMA in Ranitidine Drug Substance and Drug Product* 2-3 (2019) [hereinafter FDA, *LC-HRMS*], https://www.fda.gov/media/130801/download; FDA, *LC-MS/MS*, *supra*, at 2-3. Dr. Najafi has not asserted that the FDA, any other regulatory body, or even any independent scientist has tested

Sept. 22 *Daubert* Hearing Tr. at 134, 143, 147. The laboratory used a reverse-phase column for testing with liquids because a HILIC column does not work well with a liquid matrix. *Id.* at 134, 148. SGF is an artificial solution used during laboratory experiments to simulate the fluids found in the human stomach.

(much less validated) the use of a HILIC column to separate NDMA from ranitidine.[26] In seeking to demonstrate that a HILIC column provides a valid separation method for ranitidine, both Dr. Najafi and the Plaintiffs point only to Emery Pharma's own records in support of method validity.[27] *E.g.,* DE 5914 at 7, 18, 25 (citing the laboratory's validation reports attached to Dr. Najafi's expert report).

Second, Dr. Najafi does not contend that using a HILIC column as a method to separate ranitidine has been peer reviewed. He acknowledged at his deposition that none of the testing that Emery Pharma conducted for this litigation has been peer reviewed or published. *E.g.,* Najafi Dep. at 562.

Third, Dr. Najafi has proffered no rates of error for any of the testing that the laboratory conducted for this litigation.[28] Fourth, Dr. Najafi has not demonstrated that using a HILIC column to separate ranitidine has garnered acceptance in any scientific community. And fifth, Emery

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[26] The Plaintiffs contend that numerous scientists from various laboratories have conducted chromatography to separate ranitidine utilizing different columns and that the Defendants' criticism of Emery Pharma's use of a HILIC column is a red herring. Defendants' Sept. 22 *Daubert* Hearing Tr. At 115, 132-33. However, the Plaintiffs do not dispute that each laboratory to have tested ranitidine has done so using some type of a reverse-phase column and that Emery Pharma stands alone in using a HILIC column for its ranitidine testing.

[27] According to FDA guidance for applicants seeking FDA approval of new drugs, a change to an FDA-approved analytical procedure, such as a change in equipment, requires revalidation and submission of the alternative procedure to the FDA. Among other things, revalidation requires demonstrating that the alternative procedure is equivalent or superior to the original procedure. *Analytical Procedures and Methods Validation for Drugs and Biologics*, *supra*, at 10-11. The Court does not suggest that this FDA guidance bound Emery Pharma, as the laboratory was not seeking drug approval. However, Emery Pharma could have tested ranitidine samples both with a reverse-phase column and a HILIC column to compare the performance of the two types of columns for separating ranitidine. Dr. Najafi does not contend that the laboratory did so for any sample of ranitidine or ranitidine API.

[28] The Plaintiffs do not maintain that the rates of error for any of Emery Pharma's testing is known or even capable of being determined. The Plaintiffs instead contend that the Defendants' argument about rates of error—that is, that variability in the laboratory's test results shows that the rates of error are likely quite high—demonstrates a misunderstanding of the concept of a rate of error. DE 5914 at 38-39 (citing DE 5698 at 31). The Court does not take a position as to whether the rates of error for the laboratory's testing are or might be high. The Defendants do not have a burden to demonstrate that the rates of error are high; rather, the Plaintiffs have the burden to demonstrate that Emery Pharma's methodologies are reliable. The rates of error for the laboratory's testing are unknown, and that fact is one of several factors that the Court may, and does, consider as part of its evaluation of the reliability of the laboratory's methodologies. *See Chapman*, 766 F.3d at 1305 (citing *Daubert*, 509 U.S. at 593-94); *see also United States v. Vitek Supply Corp.*, 144 F.3d 476, 485 (7th Cir. 1998) (explaining that "the purpose of an inquiry into error rates is to determine whether tests are accurate and reliable").

Pharma switched to using a HILIC column, as an alternative to a reverse-phase column, for the purpose of its testing for this litigation. *See* Najafi First Rebuttal Report at 9.

In addition to Dr. Najafi's failure to establish that a HILIC column provides a reliable method to separate NDMA from ranitidine, he also has not demonstrated that Emery Pharma's method of chromatography would not cause NDMA to form. The Defendants and their experts have raised the concern that, if a HILIC column does not sufficiently separate ranitidine before a sample enters the mass spectrometer, then the heat that is applied to enable the mass spectrometer to analyze the sample may cause NDMA to generate. *E.g.,* Guengerich Supplemental Report at 7-9; Olsen Supplemental Report at 3-4. The Defendants' experts cite authority to demonstrate the validity of this concern. *E.g.,* EMA-Official Medicines Control Laboratory, *Test Method for the Determination of NDMA by LC-MS/MS in Ranitidine Drug Substance and Film Coated Tablets* 4 (2019) ("By conducting this procedure, a contamination of the mass spectrometer with active ingredient can be avoided. This is important since ranitidine is able to generate NDMA *in situ*.").

Dr. Najafi was asked during his deposition about the possibility that Emery Pharma's method of chromatography could cause NDMA to form. *See* Najafi Dep. at 517. In response to that question, he offered three reasons to show that the laboratory's chromatography method did not generate NDMA. The Court therefore examines each of those three reasons.

The first reason that Dr. Najafi offered was that the LC-MS/MS chromatography process applies heat for only 20 milliseconds, as compared to the 10-minute period of heating during gas chromatography that has been shown to cause NDMA to generate. *Id.* at 518 ("We go through 20 milliseconds, whereas in generation of NDMA and GC-MS, we needed 10 minutes of heating."). According to Dr. Najafi, "If you actually heated it less, you would regenerate less NDMA." *Id.* at 518-19. Dr. Najafi pointed to no source to demonstrate that 20 milliseconds are an insufficient

period of time for heat to cause NDMA to form. Dr. Najafi's explanation could at most show that Emery Pharma's chromatography method would generate less NDMA than would a gas chromatography method, due to the much briefer period of time during which the laboratory applied heat to a sample. But his explanation does not demonstrate that the laboratory's method did not cause NDMA to form.

The second explanation that Dr. Najafi offered was that, if Emery Pharma's method of chromatography did cause NDMA to generate, he expected that the method would do so consistently across all of the ranitidine samples that the laboratory tested, and he did not see evidence of consistent NDMA generation. *Id.* at 519 ("If it was being formed, it would be consistent, right? 150 milligram, you're going to get . . . let's say, a thousand nanogram, or you're going to get 5 nanograms. You get it consistently."). Dr. Najafi pointed to no source in support of his expectation that NDMA formation, were it to occur, would do so consistently across all samples of ranitidine. He did not indicate that he conducted any testing or research to confirm his theory about the consistency of NDMA formation. He has not demonstrated that his theory about consistency is more than mere speculation. *See Chapman*, 766 F.3d at 1306 (explaining that a court performing a *Daubert* analysis must determine whether the proffered expert is offering evidence that is genuinely scientific or unscientific speculation).

The third reason that Dr. Najafi offered was that a company that sells chromatography equipment had already investigated the issue and disproven the proposition that Emery Pharma's chromatography method could generate NDMA. Dr. Najafi stated that this company had published a note on the topic. Najafi Dep. at 520 ("And their note effectively looks at this. . . . [T]hey actually look at the separation and say, well, we wonder if the . . . ranitidine might actually degrade and form NDMA, and they have actually already shown that, that it doesn't."). At the Court's request,

following the *Daubert* hearings the Plaintiffs provided to the Court the note to which Dr. Najafi was referring. This note explains that separation of ranitidine API from its impurities during chromatography is "critical" to prevent the API from interfering in the analysis of the impurities. Mary E. Lame & Lindsay Hatch, Waters Corp., *High Sensitivity Quantitation of Nitrosamine Genotoxic Impurities: LC-MS Analysis of Ranitidine Drug Product Using the Waters ACQUITY UPLC I-Class/Xevo TQ-XS Tandem Quadropole Mass Spectrometer* (2020). The note proposes a method of chromatography using a particular reverse-phase column, which the authors state provides "excellent reversed-phase chromatographic retentivity of NDMA, and resolution from the drug product ranitidine." *Id.* ("Use of the reversed-phase HSS T3 Column provided excellent retentivity for nitrosamine impurities, particularly the most polar nitrosamine, NDMA, while also providing separation from ranitidine API."). The note does not indicate that insufficiently separated ranitidine would not generate NDMA. Nor does the note provide information about the use of a HILIC mode of separation to conduct chromatography with ranitidine. This note does not support Dr. Najafi's position that Emery Pharma's method of chromatography did not cause NDMA to form.

Dr. Najafi has not provided an explanation supported with anything other than his *ipse dixit* to demonstrate that Emery Pharma's method of chromatography did not generate NDMA. An "expert opinion is inadmissible when the only connection between the conclusion and the existing data is the expert's own assertions." *McDowell*, 392 F.3d at 1300; *see also Joiner*, 522 U.S. at 146 ("[N]othing 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.").

In conclusion, the Plaintiffs have not satisfied their burden to show that Emery Pharma's method of chromatography, using a HILIC column, provided a reliable methodology to measure

the NDMA in the ranitidine and ranitidine API samples that the laboratory tested for this litigation. The Plaintiffs' failure to satisfy this burden factors into the Court's evaluation under *Daubert* of the totality of the evidence and factors into the reliability of Emery Pharma's testing and the admissibility of Dr. Najafi's expert opinions based on that testing.

Emery Pharma's Chromatography Integration

Dr. Najafi has not demonstrated the reliability of the methodology of Emery Pharma's chromatography for another reason. The Court now turns to the subject of manual integration, a process by which a laboratory analyst may manipulate the results of chromatography by adjusting the area under a peak on a chromatogram, with that area representing the quantity of a component that was in the analyte. *See* McDowall, *supra* (describing manual integration as "a powerful data manipulation tool"). The topic of manual integration is of significance here, given that one of Dr. Najafi's tasks was to quantify the NDMA in samples of ranitidine and ranitidine API. *See* Najafi Report at 4.

Neither the Plaintiffs nor Dr. Najafi dispute that Emery Pharma's analysts made manual integrations while processing the results of the chromatography that the laboratory conducted for this litigation. In fact, the Plaintiffs have not disputed that "many" of the laboratory's integrations were manual.[29] *See* DE 5698 at 44. Instead, both the Plaintiffs and Dr. Najafi contend that Emery Pharma's manual integrations were justified. Dr. Najafi discussed the laboratory's manual integrations during his deposition. He explained that the presence of an asterisk on a chromatogram indicates that an analyst performed manual integration. Najafi Dep. at 434-36.

[29] During oral argument, the Court twice inquired of the Plaintiffs how the Court might get a sense of the extent of Emery Pharma's manual integrations and whether manual integration was conducted more frequently for some of the laboratory's studies than for others. Defendants' Sept. 22 *Daubert* Hearing at 155-57. The Plaintiffs did not explain how the Court might ascertain the extent of the laboratory's manual integrations. Instead, the Plaintiffs responded by stating that it was not possible to provide the Court Emery Pharma's chromatograms and that it is typical for laboratory analysts to conduct manual integration. *Id.* at 156-58.

Dr. Najafi testified that there must be a methodology to manual integration. *Id.* at 445 (stating that "the manual integration has to have a methodology."). In that respect, he is in agreement with the sources on manual integration that the parties cited in their briefing and that the Court has cited above. *See* McDowall, *supra* (explaining that it is critical for a laboratory to have written, standardized procedures that establish the circumstances under which manual integration is permitted and how it should be performed); Newton & McDowall, *supra*, (stating that manual integration should be performed only under conditions described in laboratory procedures). Dr. Najafi further testified that Emery Pharma's analysts follow a methodology for conducting manual integration. Najafi Dep. at 444-45 (explaining that "there is a methodology for integrating the area under the peak" and that "our team follows that methodology"). Dr. Najafi's assertion that laboratory analysts followed a methodology is not, in and of itself, sufficient to establish reliability for the purpose of a *Daubert* analysis. *See McClain*, 401 F.3d at 1244 ("The expert's assurances that he has utilized generally accepted scientific methodology are insufficient." (alteration omitted) (quoting *Moore v. Ashland Chem. Inc.*, 151 F.3d 269, 276 (5th Cir. 1998))); *Daubert v. Merrell Dow Pharms., Inc.*, 43 F.3d 1311, 1316 (9th Cir. 1995) (explaining that an expert's self-serving assertions that his conclusions were derived through a scientific method are not conclusive for establishing reliability).

Dr. Najafi was asked during his deposition to identify the methodology that the laboratory follows for manual integration. In attempting to respond to this line of questioning, he gave a variety of answers. First, he was asked whether the methodology was explained in a document that had been produced to the defense during the discovery process in this litigation. Najafi Dep. at 445. He responded that there was no document explaining Emery Pharma's methodology for manual integration. *Id.* at 445 ("This is not a document. This is basically a methodology. It's

really best practices for integration of the peak."). He suggested that the methodology could be found by performing a Google search of the words "controlling chromatographic integration."[30] *Id.* at 445-46 ("You can actually Google 'controlling chromatographic integration' and there is – you know, there is scientific methodology by which you do the integration.").

Next, Dr. Najafi stated that he believed that Emery Pharma follows guidance on manual integration from Agilent, the company that manufactures equipment that Emery Pharma uses to conduct chromatography. *Id.* at 447 ("I believe we used the Agilent guidance as to best practices."). He testified that Emery Pharma's employees typically receive training from Agilent when the laboratory purchases new equipment. *Id.* ("We typically, when we have a new instrument, you know, from Agilent, we get proper training from Agilent."); *id.* at 448 ("I typically look at integration and I see they're following a methodology which has been taught to them by [the] Agilent team when they install the equipment."). Dr. Najafi did not point to any document from Agilent on the subject of manual integration. Nor did he point to written laboratory procedures that would instruct Emery Pharma's analysts either where to look for guidance on the subject or to follow Agilent's guidance on the subject. When asked whether he could produce any training material instructing Emery Pharma's analysts to consult Agilent's website for procedures on manual integration, Dr. Najafi responded that he had no such material. *Id.* at 448-49 ("No, I don't have anything at my fingertip, but like I said, we follow Agilent's guidance for proper use of their mass spectrometry equipment.").

[30] The Court performed a Google search as Dr. Najafi suggested. The very first search result to appear was the article by McDowall titled *Controlling Chromatographic Integration to Ensure Data Integrity* that the Court has cited above. That article does not provide any specifics about when or how a laboratory should conduct manual integration. The article does, however, expressly advise, "A laboratory-wide standard operating procedure (SOP) for integration should establish when manual integration is justifiable and how it should be performed in a way that is most sound." The article emphasizes that point again by stating, "A written SOP is required, and must clearly define when and to what degree intervention in the automated integration system is allowed, and how it should be performed."

Then, Dr. Najafi suggested that, because Emery Pharma's analysts underwent the training needed to earn a Ph.D., the analysts were taught the methodology for manual integration as part of their education and do not need further guidance or training on the subject. *Id.* at 447-48 (testifying that "the Ph.D. scientists who do this kind of work, they have been doing it for years and years, so . . . many of them do not need any training"); *id.* at 448 ("And if we have a junior analyst, we typically put him through some proper training, you know, but, you know, almost 99 percent of the work that was done for the plaintiffs were done by highly, highly trained, talented Ph.D. scientists."); *id* at 450 ("[T]here's a methodology that they follow, and this is part of their training in graduate school, in their Ph.D. program. Many of them have done a lot of work. They have done postdoctoral work in this area and also their years of experience as well."). Dr. Najafi did not point to any sources, such as textbooks, where one might find a methodology for manual integration that is taught to students and followed by Emery Pharma analysts.

Finally, Dr. Najafi explained that Emery Pharma permits its analysts to use their own judgment to make manual integrations. Analysts were allowed to use their judgment when manually integrating the results of the chromatography that the laboratory conducted for this litigation.[31] *Id.* at 441 ("That's where NDMA is coming from in his scientific judgment and that's where he's integrating. He could have also integrated some of the yellow peaks, which would have shown much higher levels of NDMA, but, you know, he makes a judgment."); *id.* at 442-43 ("Again, it's the manual integration to—per the analysts' expertise, and they know mass spec a lot better than I do and they make a decision that this green area effectively—probably [the] computer picked some portion of that and they probably made some adjustment to make sure that we're

[31] During oral argument, the Plaintiffs reiterated that performing manual integration was a matter left to the laboratory analysts' judgment. *E.g.,* Defendants' Sept. 22 *Daubert* Hearing Tr. at 68 (explaining that it "is the judgment of the expert as to where that line is drawn"); *id.* at 69 (stating that "the analyst has to make that call").

going—we're at the right region."); *id.* at 452 ("It's—if you can—if you see the integration is done in such a—you know, the analyst's decision to actually, you know, show, you know, basically a peak integration at a slant, and that's his decision."). Through this exercise of judgment, analysts reach the chromatography results that they deem "acceptable." *Id.* at 449 ("Like I went through, we—the instrument does the integration at first, and then we look at it. If it's acceptable, we're done. If it's not acceptable, then we go through adjustments."). Dr. Najafi did not provide any explanation of what factors or considerations might guide decisions about when or how to perform manual integration. He also did not provide any explanation of what might differentiate an "acceptable" test result that does not require further integration from an unacceptable one that does.

What Dr. Najafi's testimony does reveal is that Emery Pharma's methodology for manual integration is to delegate the decisions about when and how to integrate to the judgment and discretion of individual analysts. Such an approach is contrary to sources on the topic of manual integration such as those that the Court has cited above. More importantly, such an approach cannot withstand a challenge under *Daubert*. The approach cannot withstand a *Daubert* challenge because it is not possible to assess the reliability of a methodology that simply leaves decisions to the expert. *See, e.g.*, *Lawrence v. Raymond Corp.*, No. 3:09 CV 1067, 2011 WL 3418324, at *7 (N.D. Ohio Aug. 4, 2001) ("An expert is not a black box into which data is fed at one end and from which an answer emerges at the other; the Court must be able to see the mechanisms in order to determine if they are reliable and helpful."), *aff'd*, 501 F. App'x 515 (6th Cir. 2012).

Two chromatograms discussed with Dr. Najafi during his deposition illustrate some of the many unresolved questions that Emery Pharma's approach to manual integration raises. Dr. Najafi was presented with a chromatogram purportedly representing the results of chromatography from

a test in which ham was placed in SGF. Najafi Dep. at 294-95; Najafi Dep. Ex. 16 at 97. This chromatogram displayed an asterisk, demonstrating that an analyst had performed manual integration. Najafi Dep. Ex. 16 at 97. Dr. Najafi testified that a vertical line in the middle of the chromatogram represented where NDMA, if present in the ham and SGF, would be expected to display as a peak. Najafi Dep. at 295 ("[Y]ou see where the line is? . . . That line in the middle of the page? . . . That's where we're expecting NDMA to come."). The fact that there was no peak at the vertical line in the middle of the chromatogram indicated that no NDMA was detected. *Id.* ("And the fact that we don't see it, it's indicative that there is no NDMA."). Consistent with this testimony, Dr. Najafi stated in his expert report that Emery Pharma did not detect NDMA during the test with the ham in SGF. *See* Najafi Report at 7.

As the next subject of questioning, Dr. Najafi was presented with a chromatogram that purportedly represented the results of chromatography after the ham had been combined with ranitidine in SGF for four hours. Najafi Dep. at 296; Najafi Dep. Ex. 16 at 103. This chromatogram also displayed an asterisk to denote manual integration and also had a vertical line in the middle of the chromatogram. Najafi Dep. Ex. 16 at 103. As with the prior chromatogram, there was no peak at the vertical line on this second chromatogram. *Id.* Although there was no peak at the vertical line, an analyst had identified the very top portion of a small peak offset from the vertical line as demonstrating that NDMA was present when the ham was combined with ranitidine in SGF for four hours. *Id.* The very top portion of the small peak was shaded in green. *Id.* (viewed at 600% magnification). Consistent with this testimony, Dr. Najafi stated in his expert report that NDMA was detected when ham was combined with ranitidine in SGF for four hours. *See* Najafi Report at 97.

Dr. Najafi did not provide explanations as to the distinction between the two chromatograms; why the second chromatogram showed the presence of NDMA while the first one did not; how or why an analyst had decided that the second chromatograph showed the presence of NDMA while the first one did not; how the analyst decided how much of the area under the small peak to the left of the vertical line on the second chromatogram represented NDMA; or how the analyst decided where to draw the baseline on the top of the peak to the left of the vertical line on the second chromatogram. In short, Dr. Najafi did not provide an explanation that could demonstrate the accuracy and reliability of the analyst's manual integration for the second chromatogram and, in turn, demonstrate the accuracy and reliability of the quantity of NDMA that Dr. Najafi reported for the ham-and-ranitidine test.[32]

Perhaps acknowledging that laboratory analysts' manual integrations may not always be accurate, Dr. Najafi testified that analysts err on the side of being conservative when they are manually integrating chromatography results. That is, the analysts draw peak baselines that, if not entirely accurate, underrepresent rather than overrepresent the quantity of a component in an analyte. Najafi Dep. at 444 ("I always see that they, in fact, err on the side of lowering the amount, the area under the peak."); *id.* at 449 (explaining that "we err on the side of, you know, basically being on the conservative side"). Dr. Najafi did not explain how he knows that analysts were conservative when manually integrating the results of the chromatography conducted for this

[32] Dr. Najafi instead challenged the second chromatogram as potentially inaccurately displaying Emery Pharma's data. *See* Najafi Dep. at 297-301. He asserted that he would need to view the data on a chromatogram using the software program that Emery Pharma uses in its laboratory, called MassHunter, to ascertain that the data was being correctly displayed. *See id.* at 302-07. Neither Dr. Najafi nor the Plaintiffs have directed the Court's attention to a chromatogram that looks different than the four-hour ham-and-ranitidine chromatogram shown to Dr. Najafi during his deposition. A comparison that appears in the record of the chromatogram shown to Dr. Najafi during his deposition and a screenshot of the data viewed on a chromatogram using the MassHunter program demonstrates that the two chromatograms look identical, with no peak displayed at the vertical lines in the middle of either chromatogram. *See* DE 5830-3 at 4.

litigation. He did not represent that he had checked all of the manual integrations to ensure that NDMA peak baselines were drawn conservatively. Nor did he provide an example of even one chromatogram that he maintained contained a conservatively drawn baseline.

Furthermore, Dr. Najafi did not point to any laboratory protocol requiring chromatography baselines to be drawn conservatively and did not explain how such a protocol, if one exists, was communicated to laboratory analysts. Dr. Najafi offers only his *ipse dixit* to establish that Emery Pharma's analysts would have drawn baselines that would underrepresent, rather than overrepresent, the NDMA levels in the ranitidine that the laboratory tested for this litigation. Such *ipse dixit* is insufficient to show that the levels of NDMA that Dr. Najafi reports were not an overrepresentation of the true NDMA levels in the samples of ranitidine that the laboratory tested. *See Joiner*, 522 U.S. at 146 ("[N]othing 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.").

Even if one were to accept as true Dr. Najafi's assertion that laboratory analysts attempted to be conservative in drawing NDMA peak baselines, the fact that analysts conducted so many manual integrations raises questions as to the reliability of Emery Pharma's chromatography. The frequent use of manual integration can signal that laboratory analysts were inadequately trained, that laboratory equipment needed to be serviced, and/or that the testing methods were flawed. *See* McDowall, *supra*; Newton & McDowall, *supra*. Here, the Plaintiffs have not disputed that "many" of Emery Pharma's integrations were manual, and Dr. Najafi did not provide an explanation for any of the many manual integrations that could rule out a flaw in the laboratory's chromatography process.

The Plaintiffs assert that the Defendants have not identified a single manual integration that an Emery Pharma analyst made that is not scientifically justifiable. DE 5914 at 29. But it is not the Defendants' burden under *Daubert* to show that the methods Emery Pharma used to achieve the data on which Dr. Najafi bases his expert opinions were unreliable. And it is not the Defendants' burden under *Daubert* to identify particular data that they believe is in error. To the contrary, it is the Plaintiffs' burden to demonstrate that the laboratory's methods and data are sufficiently reliable. *See Hendrix II*, 609 F.3d at 1194 (stating that the proponent of expert testimony bears the burden of showing by a preponderance of the evidence that the expert's methodology is sufficiently reliable).

For all of the reasons discussed above, the Plaintiffs have not met that burden. Their failure to establish that Emery Pharma performed manual integration pursuant to a reliable methodology factors into the Court's evaluation under *Daubert* of the totality of factors weighing upon the reliability of the laboratory's testing and the admissibility of Dr. Najafi's expert opinions based on that testing.

b. **Documentation**

Another issue in this litigation is whether Emery Pharma followed generally accepted standards for documenting the work that it performed. In addition to identifying validation as a prerequisite of analytical procedures used to assess drug stability, the USP lists sound record keeping as another laboratory "prerequisite." *USP General Chapter <1010>*, *supra*, at 2; *see also Bioanalytical Method Validation*, *supra*, at 18 ("General and specific [standard operating procedures] and good record keeping are essential to a properly validated analytical method."). Laboratory records should be "maintained with sufficient detail, so that other equally qualified analysts can reconstruct the experimental conditions and review the results obtained." *USP*

General Chapter <1010>, *supra*, at 2. "Study protocols and data analyses should be adequately documented so that a reviewer can understand the bases of the study design and the pathway to study decisions." *Id.* at 2.

The Scientific Working Group on Quality Practices in Basic Biomedical Research is a group sponsored in part by the World Health Organization consisting of scientists from around the world. This Scientific Working Group similarly has stressed the need for sound laboratory record keeping. The Scientific Working Group states in a handbook on quality practices for biomedical research:

> Making a full record of all information is essential not only to permit appropriate scientific interpretation of the results but also to enable complete reconstruction of the study, should this be necessary. Documentation is the only way of demonstrating what actually went on at the time of the experiment. *Without documentation the process is meaningless; essentially there has been no study.* As well as containing the data generated, the study records must provide that all the required procedures were correctly carried out at the stipulated time. If complete records are not made, the study validity is compromised. Missing data suggests that either the procedure concerned was never performed or that the data have been lost. In either case the study is seriously compromised and may have to be repeated from scratch.

Scientific Working Group on Quality Practices in Basic Biomedical Research, *Handbook: Quality Practices in Basic Biomedical Research* 35-36 (2005).

In describing quality practices for laboratory record keeping, the Scientific Working Group distinguishes between prescriptive documents and descriptive records. Prescriptive documents are created in preparation for a study, and they give instructions for what is to happen during the study. *Id.* at 36. Prescriptive documents include study plans and standard operating procedures. *Id.* Descriptive records describe what actually happened during a study. *Id.* They include study reports, raw data, and derived data. *Id.* A research institution should maintain both prescriptive documents and descriptive records. *Id.* at 37.

According to the Scientific Working Group, every study must have one type of prescriptive document called a study plan or study protocol.[33] *Id.* The study protocol should "describe the study design in detail, including the purpose, intended methods, and names of persons who will carry out the study and interpret the experimental data" and should "be sufficiently detailed to enable the study to be repeated exactly, if necessary." *Id.* at 38; *see also Analytical Procedures and Methods Validation for Drugs and Biologics*, *supra*, at 4 ("You should describe analytical procedures in sufficient detail to allow a competent analyst to reproduce the necessary conditions and obtain results within the proposed acceptance criteria."). Among other things, a study protocol should detail the "test material and conditions for its handling and storage," "type and quality of reagents and equipment," "type of test system and how it is to be handled," "[p]roposed dates for key events," "observations to be made," "methods for data collection, evaluation, verification and (if appropriate) statistical analysis," and "methods for reporting and achieving results." *Quality Practices in Basic Biomedical Research*, *supra*, at 38; *see also Analytical Procedures and Methods Validation for Drugs and Biologics*, *supra*, at 4-5 (listing "essential information" to include in an analytical procedure, including a "step-by-step description of the method"). Because the study protocol "is the key document for communicating the intentions of the study to all contributing staff and sponsors, its contents and layout should be clear." *Quality Practices in Basic Biomedical Research*, *supra*, at 37.

Another type of prescriptive document is one listing laboratory standard operating procedures. *Id.* at 40. Standard operating procedures "provide instructions for activities of a repetitive, routine nature in a very detailed manner." *Id.* Procedures that a laboratory performs

[33] "Study plan" and "study protocol" are used interchangeably to describe the same type of document. Because the parties refer to protocols throughout their briefing, the Court likewise uses that term in this Order.

routinely may be described in full in standard operating procedures, rather than in each study's protocol. *Id.* at 39.

The Scientific Working Group explains that descriptive records show what was done, how it was done, who did the work, and when the work was performed. *Id.* at 43. Descriptive records should demonstrate compliance with the study protocol and the relevant standard operating procedures. *Id.* One type of a descriptive record is a laboratory notebook. A notebook is used to record all activities undertaken as a study progresses. *Id.* at 45-46. Ideally, a separate notebook should be used for each study. *Id.* at 46. Mixing multiple studies in one notebook makes it difficult to trace any one study. *Id.* If multiple notebooks are used, they should be consecutively numbered. *Id.* All of the pages of a notebook should be numbered, and the notebook should contain an index that reflects its contents. *Id.* at 46-47. Daily entries and any corrections in a notebook should be signed and dated. *Id.* at 47.

These various sources provide standards for laboratory documentation and emphasize the importance of documenting scientific research in a way that will permit other scientists to reproduce the research. Reproducibility is one of the hallmarks of reliable scientific testing and is pertinent to an analysis under *Daubert*. *See* 509 U.S. at 593 ("[A] key question . . . is . . . whether [a scientific theory or technique] can be (and has been) tested. Scientific methodology today is based on generating hypotheses and testing them to see if they can be falsified; indeed, this methodology is what distinguishes science from other fields of human inquiry" (internal quotation marks and citation omitted)); *Zenith Elecs. Corp. v. WH-TV Broad. Corp.*, 395 F.3d 416, 419 (7th Cir. 2005) ("An expert must offer good reason to think that his approach produces an accurate estimate using professional methods, and this estimate must be testable. Someone else using the same data and methods must be able to replicate the result."); *United States v. Hebshie*, 754 F.

Supp. 2d 89, 125 (D. Mass. 2010) ("Documentation is necessary to test a hypothesis; in fact, reproducibility is the sine qua non of 'science.'").

Recognizing the importance of sound documentation, courts across the country have excluded expert opinions based on scientific testing where the testing was inadequately documented to permit scrutiny and replication in the scientific community. In *Barnext Offshore, Ltd. v. Ferretti Group USA, Inc.*, for example, a court excluded under *Daubert* an expert's opinion about the cause of a fire where the opinion was based on a self-conducted burn test that involved the expert applying a propane torch to components of an air conditioning unit to see whether they would catch on fire. No. 10-23869-CIV, 2012 WL 13012778, at *10 (S.D. Fla. May 24, 2012). The court determined that the results of the burn test were inadmissible because the test was incapable of being replicated due to the expert's failure to document key aspects of the test, such as how the expert controlled the torch's temperature, what that temperature was, the duration of time that the expert applied the torch to the air conditioning unit components, and the temperature of the components when the torch was applied. *Id.* Similarly, in *Morehouse v. Louisville Ladder Group. LLC*, a court excluded under *Daubert* an expert's opinion about the weakness of a ladder where the opinion was based on testing that the expert had conducted with a sample ladder. No. Civ.A. # 3:03-887-22, 2004 WL 2431796, at *5-8 (D.S.C. June 28, 2004). The court explained that the expert failed to record critical details of the test that were needed to permit the test to be scrutinized by the scientific community, such as the number of ascending and descending trips taken on the ladder and the weight placed on the ladder. *Id.* at *7; *see also Rembrandt Vision Techs., L.P. v. Johnson & Johnson Vision Care, Inc.*, 282 F.R.D. 655, 667 (M.D. Fla. 2012) (excluding an expert's opinion based on testing of contact lenses where the testing "was not reproducible because [the expert] failed to document and disclose the procedures he used to

conduct his tests," which "strongly weigh[ed] against the reliability" of the expert's methodology), *aff'd*, 725 F.3d 1377 (Fed. Cir. 2013); *Snoznik v. Jeld-Wen, Inc.*, No. 1:09cv42, 2010 WL 1924483, at *13 (W.D.N.C. May 12, 2010) (excluding an expert's opinion based on testing on a window because the expert's lack of documentation made it impossible for others in the scientific community to replicate the test).

i. Parties' Arguments

The Defendants argue that Emery Pharma did not follow generally accepted standards for documenting the work that it performed for this litigation. DE 5698 at 9, 47. The laboratory did not follow any standard operating procedures when conducting its ranitidine testing. *Id.* at 21, 40-41. The laboratory's study protocols inadequately explain how any study was to be conducted. *Id.* at 10, 46-47, 50. Moreover, several of the studies lack protocols altogether. *Id.* at 9-10. Emery Pharma's descriptive records do not show how studies were conducted and do not contain all of the testing data.[34] *Id.* at 10, 46-48, 50. And it is impossible to trace the data that does appear in the descriptive records to the levels of NDMA that Dr. Najafi reports. *Id.* at 10, 47-49.

The Plaintiffs contend that Emery Pharma maintained both types of records and meticulously documented its testing. DE 5914 at 43. The laboratory created detailed protocols that describe the instrumentation, parameters, and steps for the studies. *Id.* at 8, 17, 26, 43-45. Analysts documented how they conducted the studies in detailed notebooks. *Id.* at 8, 45. The Defendants received through discovery comprehensive records and data for all of Emery Pharma's testing. *Id.* at 8, 45-46, 48.

[34] In a separate motion, the Defendants seek to have Dr. Najafi stricken as an expert due to the Plaintiffs' purported failure to produce through discovery the complete documentation for Emery Pharma's testing. *See* DE 5694.

ii. Analysis

The Court turns to the matter of prescriptive documents and descriptive records, as part of standard operating procedures.

Emery Pharma's Prescriptive Documents

Emery Pharma did not utilize standard operating procedures when conducting the ranitidine testing for this litigation. Dr. Najafi testified that the laboratory had no standard operating procedures that it applied to the testing conducted for this case. Najafi Dep. at 48 (testifying that "there were no [standard operating procedures] provided to us by the – by anybody or by the government or by ourselves"); *id.* at 506 (explaining that "[w]e do not have [standard operating procedures] with our research investigations work").

According to the Scientific Working Group, in the absence of standard operating procedures for the ranitidine testing for this litigation, the descriptions and instructions for each individual study should be detailed in a study protocol. *Quality Practices in Basic Biomedical Research*, *supra*, at 37-39 (explaining that every study must have a plan or protocol but that routine laboratory procedures may be described in standard operating procedures, such that "the study plan need not explain such procedures in full detail but could instead reference the relevant [standard operating procedures]"). The Court therefore examines Emery Pharma's study protocols, their prescriptive documents.

Dr. Najafi attaches six protocols to his expert report and one additional protocol to his rebuttal report. *See* DE 5698-10 at 140-66; DE 5698-11 at 28-32. According to the Plaintiffs, these attached protocols comprise the full set of protocols for the testing that Emery Pharma conducted for this litigation. *E.g.,* DE 5914 at 26 (explaining that the "detailed protocols, which appear in

Appendix A to Dr. Najafi's report, provide specific parameters for each test and specify the exact steps the analysts followed in conducting the tests").

A review of the protocols attached to Dr. Najafi's reports reveals that some of the studies that Emery Pharma undertook for this litigation lacked protocols. For example, Dr. Najafi discusses in his expert report a "long term refrigeration stability study" in which a ranitidine product was placed in a refrigerator for nine months, and tablets were periodically tested for the presence of NDMA. Najafi Report at 61-62. Dr. Najafi has not attached to his reports a protocol for this refrigeration study. As another example, Dr. Najafi discusses in his expert report "testing to assess NDMA content uniformity" where multiple ranitidine tablets from a container were tested to determine the degree of uniformity of NDMA levels among the tablets. *Id.* at 67-68. Dr. Najafi has not attached to his reports a protocol for this study.

The Court questioned the Plaintiffs about the studies lacking protocols during oral argument. Using the refrigeration study as an example, the Court asked whether the Plaintiffs could identify authority standing for the proposition that such a study would not require a protocol. Defendants' Sept. 22 *Daubert* Hearing Tr. at 166-67. The Plaintiffs did not point to any authority supporting that proposition. Instead, the Plaintiffs responded that whether a study needs a protocol "depends on the study." *Id.* at 167. The Plaintiffs maintained that the refrigeration study did not require a protocol because it simply "involved taking the product and putting it in a refrigerator at 4 degrees" and was conducted to verify that GSK was correct in its contention that refrigerating ranitidine stops NDMA from forming. *Id.* at 167-68.

In addition, the protocols that Dr. Najafi has disclosed do not provide a level of detail that would "enable the study to be repeated exactly." *See Quality Practices in Basic Biomedical Research*, *supra*, at 38. Take for instance the protocol that Dr. Najafi provides for the laboratory's

baseline testing. *See* DE 5698-10 at 140-45. This study involved testing tablets from 254 ranitidine products, as well as ranitidine API, for the presence of NDMA. Emery Pharma obtained the samples that it tested from some of the Defendants. *See* Najafi Report at 62-66. The protocol for the baseline testing did not specify which products would be tested, how many products would be tested, or how many tablets from each product would be tested.

Dr. Najafi was asked about the selection of the samples for baseline testing during his deposition. He testified that he could not say whether Emery Pharma tested tablets from every ranitidine product that the laboratory received from the Defendants. Najafi Dep. at 366 ("I cannot tell you with 100 percent certainty that we've done baseline . . . testing on every sample. But I can tell you with good certainty that [a] majority of them have been tested for baseline testing."). Dr. Najafi stated that, rather than testing all of the products that the laboratory received from the Defendants, Emery Pharma "tried" to test samples that would be "representative" of drug product from different lots, batches, and manufacturers and that had previously been stored at different storage facilities. *Id.* ("We tried to test representative samples from different lots, different batches, different manufacturers, you know, that were coming from different locations."); *id.* at 367 ("So we have so many different samples and we tried to make sure that we get those tested that come from various location[s], various manufacturers . . . ."). Dr. Najafi did not explain how analysts would ascertain whether they had tested "representative" samples. Nor did he explain how analysts would ascertain that they had tested a sufficient number of samples, such that the baseline testing could be considered "representative" and therefore complete. And neither the instruction to test representative samples nor an explanation of how one would determine representativeness is included within the protocol for the baseline testing. Dr. Najafi's testimony revealed that, rather than having a prespecified plan for which products to test, he ultimately left sample selection to

the analysts. *Id.* at 366-67 ("So we—I left it really up to . . . the analysts, my team, to—but what I instructed them was I wanted a very good cross-section of locations, batch numbers, manufacturers, and that's what we did."). The protocols attached to Dr. Najafi's report for other studies suffer from the same deficiency: a lack of explanation about which and how many samples to use for testing. *See, e.g.*, DE 5689-10 at 146-53 (protocols for simulated consumer experience and SGF testing).

As another example of a deficiency in Emery Pharma's protocols, Dr. Najafi attached to his report a protocol for a study in which food would be combined with ranitidine in SGF, a study which the Court discusses in greater detail below. *See* DE 5698-10 at 148-53. The protocol for this study did not specify which types of food were to be utilized. And, in fact, the full extent of the laboratory's experimentation with food is still not clear from the record. Dr. Najafi states in his expert report that ham, bacon, hotdog, and sausage were used for the SGF study, Najafi Report at 94, but laboratory records indicated that additional products such as smoked salmon and coffee were also studied. Najafi Dep. Ex. 9 at 31, 42. The study protocol did not prespecify the foods that were to be the subject of the study.

Emery Pharma's Descriptive Records

The Plaintiffs maintain that Emery Pharma's analysts detailed what they did for each study in one type of descriptive record, that is, laboratory notebooks. DE 5941 at 8, 45. The Court therefore has examined one such notebook, notebook number 078-RC, which was admitted as an exhibit during Dr. Najafi's deposition. *See* Najafi Dep. Ex. 9. A review of that notebook demonstrates that the notebook would not permit an independent scientist to track the progression of a study or to replicate a study. *See USP General Chapter <1010>*, *supra*, at 19 (requiring

laboratory records to be maintained with sufficient detail to permit qualified analysts to review results and to reconstruct experimental conditions).

The notebook is not dedicated to a single study, but rather mixes together protocols, notes, results, and charts relating to multiple studies. And the notebook does not appear to be organized in any logical way. For example, page 20 of the notebook contains graphs of just a few of the results from two different studies, and then the very next page contains a portion of what looks to be a protocol for a third study. Najafi Dep. Ex. 9 at 30-31. Locating the entirety of the notebook entries for any one study would necessitate reviewing all of the notebooks that Emery Pharma maintained and potentially cobbling together various pages from various notebooks.

Moreover, the notebook does not make it possible to track what actually was done for any single study. Printed portions of study protocols have been pasted into the notebook, for example on page 21 for the study of ranitidine and food in SGF. *Id.* at 31. But the notebook does not indicate whether analysts actually followed those protocols or otherwise demonstrate each of the steps that analysts took to conduct each of the studies.[35] *Cf. Barnext*, 2012 WL 13012778, at *10 (excluding the results of an expert's testing when insufficient information existed about how he conducted the test to permit replication); *Morehouse*, 2004 WL 2431796, at *7 (excluding the results of an expert's testing when he failed to document critical details about how he conducted the test to permit the scientific community to scrutinize his work and the court to evaluate reliability).

Furthermore, Dr. Najafi has not demonstrated that a scientist could trace test results that appear in the notebook to the results that Dr. Najafi has included in his expert report. Dr. Najafi

[35] Emery Pharma maintained five notebooks for the testing it conducted for this litigation. The Court has likewise reviewed the other four notebooks. These other notebooks similarly would not permit an outside scientist to track the progression of a study or to replicate a study. *See* DE 5755-4 at 2-47, 115-213.

was questioned about the traceability of Emery Pharma's data during his deposition. As an example of such questioning, he was presented with page 14 of notebook 078-RC, a page containing a date of October 13, 2021, and indicating that it is related to the laboratory's baseline testing. Najafi Dep. Ex. 9 at 24; Najafi Dep. at 381. Page 14 lists data for 48 "[s]ample[s]." Najafi Dep. Ex. 9 at 24. For every sample, two numbers are listed that purportedly correspond with levels of NDMA detected in the sample, and an "[a]verage" of those levels is also listed. *Id.*

During his deposition, Dr. Najafi was directed to two particular samples listed on page 14 of the notebook: samples 1 and 41. Najafi Dep. at 387-38, 401. Sample 1 lists 376.5 and 440.0 and an average of 410.2; sample 41 lists 322.0 and 318.7 and an average of 320.4. Najafi Dep. Ex. 9 at 24. Dr. Najafi was then asked about where these numbers are found in the chart of the results for the baseline testing that he attached to his expert report as Appendix B. *See* DE 5698-10 at 172-78; Najafi Dep. at 317 (acknowledging that Appendix B contains the results of all of the baseline testing). Dr. Najafi was directed to two entries on the Appendix B chart listing a testing date of October 13, 2021, and reporting "Average NDMA Level[s]" of 410.2 and 320.4 (the same testing date and average NDMA levels listed for samples 1 and 41 on page 14 of the notebook). *See* DE 5698-10 at 176; Najafi Dep. at 397, 402. However, the levels of NDMA detected—the numbers purportedly used to calculate that "average"—were different on the Appendix B chart than the NDMA levels appearing on page 14 of the notebook. *Compare* Najafi Dep. Ex. 9 at 24, *with* DE 5698-10 at 176.

Dr. Najafi did not point to any document demonstrating that samples 1 and 41 from the notebook were not the same samples that corresponded to the two chart entries to which he was being directed to explain, although he did state that he would need to check laboratory records to

confirm the sample lot numbers.[36] Najafi Dep. at 403. Further, Dr. Najafi did not explain why, if samples 1 and 41 listed in the notebook do correspond to the chart entries, the NDMA levels listed in the notebook were different than the NDMA levels listed on the chart.

The Plaintiffs likewise do not point the Court to any document demonstrating that samples 1 and 41 from the notebook are not the same samples that correspond to the chart entries discussed during Dr. Najafi's deposition. The Plaintiffs do, however, attempt to explain why the levels of NDMA listed in the notebook would be different than the NDMA levels listed in Appendix B to Dr. Najafi's expert report. The Plaintiffs assert that the levels in the notebook are "*preliminary* NDMA values" and that "these results preceded the final interpretations by analysts" to reach the results that Dr. Najafi included in his expert report. DE 5914 at 47. But the Plaintiffs do not provide the Court with any laboratory documentation to show how or why the preliminary values in the notebook were changed to reach the final values in Dr. Najafi's expert report or to otherwise demonstrate the reliability of those changes to NDMA levels.

Despite asserting that Emery Pharma's work satisfies the highest standards and is reproducible and publishable, during his deposition Dr. Najafi could not name the particular standards that the laboratory's documentation for this litigation has satisfied. *E.g.,* Najafi Dep. at 136 ("Everything we do at Emery Pharma meets the highest generally accepted scientific principles. Everything. And it's done to publication standards."); *id.* at 140 (responding, when asked about the standards to which he was referring, "So these are . . . generally accepted scientific principles. They're not written anywhere that I can go to and point to you, but these are – your

[36] Dr. Najafi also indicated that he would need the assistance of Emery Pharma analysts to enable him to answer questions about tracing the laboratory's data. Najafi Dep. at 115 ("I can get it done on our computer with the help of my analyst, we can easily find that within minutes. . . . I don't know how he would do it, but we have the ability to quickly get that searched and found."). The Court addresses Dr. Najafi's reliance on laboratory analysts in the following section.

method needs to be reproducible, repeatable."); *id.* at 348 ("[W]e comply with guidances [sic] that relates to the work we do. There are thousands of guidances [sic] that do not apply to us."). Dr. Najafi's assertions that Emery Pharma's documentation satisfies the highest standards do not establish that the documentation does indeed do so. An "expert's assurances that he has utilized generally accepted scientific methodology are insufficient." *McClain*, 401 F.3d at 1244 (alteration omitted) (quoting *Moore*, 151 F.3d at 276) ("O'Donnell attempts to anoint his opinions by claiming that he based them on the 'broad principles of pharmacology.' In the *Daubert* context, such phrases have little value.").

Under *Daubert*, Emery Pharma's testing should at a minimum be documented in such a way as to enable it to be replicated. *See, e.g.*, *Zenith Elecs. Corp.*, 395 F.3d at 419 ("Someone else using the same data and methods must be able to replicate the result."); *Hebshie*, 754 F. Supp. 2d at 125 ("Documentation is necessary to test a hypothesis; in fact, reproducibility is the sine qua non of 'science.'"). For all of the reasons that the Court has discussed, including studies lacking protocols, study protocols lacking information, and an inability to track the progression and results of a study, the Plaintiffs have not carried their burden to demonstrate that the testing that Emery Pharma conducted for this litigation is capable of replication. Their failure to carry this burden factors into the Court's evaluation under *Daubert* of the totality of the evidence and weighs upon the reliability of the laboratory's testing and the admissibility of Dr. Najafi's expert opinions based on that testing.

c. **Reliance on Assistants**

Another issue in this litigation is how Dr. Najafi left operational decisions to the professional judgment of his employees. "An expert witness is permitted to use assistants in formulating his expert opinions, and normally they need not themselves testify." *Dura Auto. Sys.*

of Ind., Inc. v. CTS Corp., 285 F.3d 609, 612 (7th Cir. 2002); *see also* Fed. R. Evid. 703 (permitting an expert to base an opinion on facts or data that the expert has been made aware of); *In re James Wilson Assocs.*, 965 F.2d 160, 172 (7th Cir. 1992) (explaining that an "expert is of course permitted to testify to an opinion formed on the basis of information that is handed to rather than developed by him—information on which he lacks first-hand knowledge"). "The opposing party can depose [the assistants] in order to make sure they performed their tasks competently; and the expert witness can be asked at his deposition whether he supervised them carefully and whether his relying on their assistance was standard practice in his field." *Dura*, 285 F.3d at 613. "Numerous courts have held that reliance on scientific test results prepared by others may constitute the type of evidence that is reasonably relied upon by experts for the purposes of Federal Rule of Evidence 703." *Hi-Tech Pharms. Inc. v. Dynamic Sports Nutrition, LLC*, No. 1:16-cv-949-MLB, 2021 WL 2185699, at *8 (N.D. Ga. May 28, 2021).

However, the "[a]nalysis becomes more complicated if the assistants aren't merely gofers or data gatherers but exercise professional judgment that is beyond the expert's ken." *Dura*, 285 F.3d at 613. "[T]he expert witness must in the end be giving his *own* opinion. He cannot simply be a conduit for the opinion of an unproduced expert." *Malletier v. Dooney & Bourke, Inc.*, 525 F. Supp. 2d 558, 664 (S.D.N.Y. 2007); *see also Hi-Tech Pharms.*, 2021 WL 2185699, at *7 (explaining that an expert "may not simply parrot the work actually done by another expert"). The expert cannot vouch for the assistants' judgment where the soundness of that judgment is at issue. *Dura*, 285 F.3d at 613. "Absent an independent opinion based upon a reliable methodology, the expert is little more than a conduit or transmitter for hearsay." *Hi-Tech Pharms.*, 2021 WL 2185699, at *7 (internal alteration and quotation marks omitted).

Applying these principles, in *Fowler v. United States*, a district court granted a motion *in limine* to exclude an agricultural economist's expert opinion about the number of days that would have been suitable for field work during a three-year period. No. 08-216, 2009 WL 2827958, at *8-9 (W.D. La. Sept. 1, 2009). The economist's opinion was based on a calculator developed and ran by a former colleague. *Id.* at *8. The results produced by the calculator formed the basis of the economist's expert opinion. *Id.* at *8-9. At one point, the economist had noticed a potential error in the calculated results, and the former colleague made a mathematical adjustment. *Id.* at *9.

The plaintiffs argued in their motion *in limine* that the former colleague was "really the expert" on the calculator and that the economist "should not be allowed to act as a mouthpiece for another expert." *Id.* The district court agreed. The district court stated, "The methods and calculations used by [the former colleague] are not accessible to the court for purposes of verification and, thus, [the former colleague] is not merely a 'gopher' or 'assistant,' but an independent expert." *Id.*

Conversely, in *Hi-Tech Pharmaceuticals Inc. v. Dynamic Sports Nutrition, LLC*, a district court denied a motion to exclude an expert's opinion that a company had intentionally spiked a dietary supplement with steroids. 2021 WL 2185699, at *8. The expert's opinion was based on chromatography testing conducted at his laboratory. *Id.* at *3-5. The plaintiff sought to exclude the expert because he had not conducted the testing himself and was merely parroting the opinions of the laboratory technician who did conduct the testing. *Id.* at *5, *7.

The district court disagreed. The district court explained that, although the technician had operated the chromatography instrumentation, he had done so using standard operating procedures that the expert himself had written. *Id.* at *7. The procedures did not permit the technicians to exercise any independent judgment or discretion. *Id.* at *3, *7. Moreover, the expert himself

analyzed the raw chromatography data to reach the conclusions that he provided in his report. *Id.* at *7. The expert's report contained "his own independent opinions based on his years of expertise and involvement developing and overseeing the testing procedures" and the fact that he had not conducted the testing personally went to the weight and credibility of his testimony but not its admissibility. *Id.* at *8.

i. Parties' Arguments

The Defendants assert that Dr. Najafi is unable to articulate why Emery Pharma's testing methods were valid because he left operational decisions to the professional judgment of his employees. DE 5698 at 18, 42. The Plaintiffs respond that reliance on laboratory analysts is routine and not a basis to strike Dr. Najafi's expert opinions. DE 5914 at 30-31.

ii. Analysis

Dr. Najafi testified during his deposition that the "team" at Emery Pharma designed the tests for this litigation and wrote the study protocols. Najafi Dep. at 130-13 (stating that "by and large, it's been a team effort" when asked whether he prepared and wrote protocols for the laboratory's ranitidine experiments). He testified that there were experiments that he "conceptualized" and "shared with the team," but he could not recall which experiments he had conceptualized. *Id.* at 131. He did not decide which analytical methods to use. *Id.* at 131-32 (responding, when asked whether he had decided which methods would be used, "[t]ypically not" and "[t]hose are often left to the analyst"). Nor was he the person who conducted the testing or, as he put it, "push[ed] the buttons." *Id.* at 111 ("So I don't go push the buttons on the instrument. I don't manipulate files. I rely on my team to handle it."); *id.* at 130 ("I used to push the button, but I haven't done that in a few—for a few years."); *id.* at 352 ("Do I push buttons right now in the lab? I don't."). Rather, Dr. Najafi relied on Emery Pharma's analysts to determine and validate

the testing methods, conduct the testing, and document their work. *Id.* at 111 ("I rely on my team to handle it."); *id.* at 132 ("I have [a] very skilled team that in many ways they know exactly what needs to be done, how it needs to be—the method needs to be validated, how the method needs to be performed."); *id.* at 133-34 (naming analysts who were "the primary team members" to make operational decisions, design the tests, and decide which methodologies to use).[37]

Dr. Najafi testified during his deposition about various matters that he left to the discretion of analysts. For example, he left the selection of the ranitidine products to be studied as part of the baseline testing to analysts. *Id.* at 366-67 ("So we—I left it really up to . . . the analysts, my team, to—but what I instructed them was I wanted a very good cross-section of locations, batch numbers, manufacturers, and that's what we did."). As another example, he left decisions about how and when to perform manual integrations to analysts. *Id.* at 441 ("That's where NDMA is coming from in his scientific judgment and that's where he's integrating. He could have also integrated some of the yellow peaks, which would have shown much higher levels of NDMA, but, you know, he makes a judgment."); *id.* at 442-43 ("Again, it's the manual integration to—per the analysts' expertise, and they know mass spec a lot better than I do and they make a decision that this green area effectively—probably [the] computer picked some portion of that and they probably made some adjustment to make sure that we're going—we're at the right region.").

The Court concludes that Dr. Najafi's heavy reliance on the judgment of analysts to develop, conduct, and document the ranitidine testing and then to interpret the results of that testing—judgment that the analysts exercised without guiding principles—is an additional factor

[37] When asked again whether he had conducted any ranitidine testing himself, Dr. Najafi stated that he "did perform a series of testing" to make sure that "the numbers [we]re correct." Najafi Dep. at 134-135; *id.* at 136 ("It was primarily just done to make sure that I'm confident of the numbers."). He did not provide any information about this test, however. He could not recall what test he had conducted, and he stated that he did not maintain any record of the test. *Id.* at 135.

weighing against the admissibility of Dr. Najafi's opinions. One issue of particular significance is Dr. Najafi's reliance on the judgment of analysts to make manual integrations. And Dr. Najafi points to no written procedures, instructions, or guidance that would inform analysts of how to perform manual integrations. Rather, he trusts the analysts to exercise their professional judgment in accordance with their education and experience. Tellingly, he testified that Emery Pharma's analysts understand manual integration "better than" he does. *See id.* at 442-43.

Dr. Najafi's use of analysts in this litigation is distinguishable from the facts in *Hi-Tech Pharmaceuticals Inc.*, where the district court permitted the expert to opine about steroids in a dietary supplement. Although the expert in that case, as here, did not conduct the chromatography himself, the chromatography at issue in *Hi-Tech* had been conducted using standard operating procedures that the expert had written and that left no room for the exercise of judgment or discretion, and the expert analyzed the raw data himself. *See* 2021 WL 2185699, at *7-8. In contrast, Emery Pharma's analysts exercised their judgment in a way that enabled them to adjust the data, without any standard procedures, and Dr. Najafi reported the analysts' adjusted results. This situation is comparable to *Fowler*, where the district court excluded the opinion of the economist who was simply parroting results developed by someone else. *See* 2009 WL 2827958, at *8-9. So too, Dr. Najafi reports the NDMA levels that the laboratory's analysts determined, through the exercise of their own judgment, that the chromatography testing had revealed.

Emery Pharma's analysts designed the tests, selected and validated the testing methods, conducted the testing, and then used their professional judgment to make manual adjustments to the data to reach results that they, in their discretion, deemed acceptable. *See, e.g.*, Najafi Dep. at 449 ("Like I went through, we—the instrument does the integration at first, and then we look at it. If it's acceptable, we're done. If it's not acceptable, then we go through adjustments."). The

analysts, not Dr. Najafi, are the experts who could explain how they achieved the results of the studies that they conducted. By reporting the levels of NDMA that the studies purportedly revealed, Dr. Najafi is serving as a conduit for the opinions of the laboratory's analysts, who have not been disclosed as general causation expert witnesses in this litigation. Dr. Najafi's heavy reliance on the discretion and judgment of laboratory analysts factors into the totality of the Court's evaluation under *Daubert* of the reliability of Emery Pharma's testing and admissibility of Dr. Najafi's expert opinions based on that testing.

d. **Peer Review**

Another issue in this litigation is whether the expert's methodology has been subjected to peer review and publication, as it is relevant to the Court's assessment of the reliability of an expert's opinion. *Daubert*, 509 U.S. at 593-94. Peer review does not necessarily correlate with reliability. *Id.* at 593. However, "submission to the scrutiny of the scientific community is a component of good science, in part because it increases the likelihood that substantive flaws in methodology will be detected." *Id.* (internal quotation marks and citation omitted); *see also Mitchell v. Gencorp Inc.*, 165 F.3d 778, 784 (10th Cir. 1999) ("By failing to subject their opinions to peer review, the experts missed the opportunity to have other scientists review their work and warn them of possible flaws in their methodology."); *Daubert*, 43 F.3d at 1318 ("That the research is accepted for publication in a reputable scientific journal after being subjected to the usual rigors of peer review is a significant indication that it is taken seriously by other scientists, i.e., that it meets at least the minimal criteria of good science.").

i. Parties' Arguments

The Defendants point out that, in addition to the fact that using HILIC as a method to separate ranitidine has not been peer reviewed, none of Emery Pharma's individual studies have

been subjected to peer review. DE 5698 at 9-10, 20, 26, 29, 32, 37, 40-41. The Plaintiffs respond that the fact that the laboratory's testing lacks peer review cannot be held against Dr. Najafi because the materials that he and Emery Pharma produced were to be used for litigation purposes only, and orders entered in this litigation preclude peer review. DE 5914 at 29-30. The Plaintiffs state that Dr. Najafi intends to submit the laboratory's work for peer review as soon as he is permitted to do so. *Id.* at 30.

ii. Analysis

It is undisputed that none of the testing that Emery Pharma conducted for this litigation has been subject to peer review. *See* Najafi Dep. at 562 (acknowledging that the testing has not been peer reviewed). Dr. Najafi testified that the lack of peer review is due to limitations that have been imposed to preserve confidentiality during the course of the litigation. *Id.* at 144 ("But we have not shared any of our data because we're on their confidentiality and this is part of a litigation, we haven't shared any of our data with the FDA."); *see also* Najafi First Rebuttal Report at 13 (stating that "the study and its results are confidential in this litigation and was not completed for purposes of a peer-reviewed publication"). Dr. Najafi further testified that he hopes that Emery Pharma's work will be published after the confidentiality limitations for this litigation have been lifted. Najafi Dep. at 561 ("And, you know, so our hope is to be able to publish once the Court order[ed] confidentiality goes away and we would be able to publish."); *see also* Najafi First Rebuttal Report at 13 (asserting that "the subject of this report and my work was conducted in conformance with the highest publication standards, and we would certainly like to publish these data once the litigation has concluded").

The Court considers the lack of peer review as part of its assessment of the reliability of Emery Pharma's methodologies. The ranitidine testing that the laboratory conducted for this

litigation has not been subjected to review by any scientist outside of this litigation or by any governmental or regulatory body. This lack of review is of particular significance because, as the Court describes in more detail below, Emery Pharma designed and conducted novel experiments for this litigation that did not follow any preexisting, peer-reviewed experimental designs, much less designs established to assess drug stability. The lack of peer review of Emery Pharma's testing factors into the Court's evaluation under *Daubert* of the totality of factors weighing upon the reliability of Emery Pharma's testing and admissibility of Dr. Najafi's expert opinions based on that testing.[38]

e. **Baseline Testing**

A further issue in this litigation is the reliability and helpfulness of particular testing on which Dr. Najafi and other Plaintiffs' experts base their opinions. The Court examines several of the testing methodologies that the laboratory conducted: baseline testing, simulated consumer experience testing, SGF testing, and additional studies that the laboratory conducted.

Baseline testing of ranitidine is intended to reveal the level of NDMA in a ranitidine product before a consumer opens the product. Defendants' Sept. 21 *Daubert* Hearing Tr. at 78-79. Given the removal of ranitidine products from the consumer market, in order to conduct its baseline testing, Emery Pharma measured the quantities of NDMA in Zantac and Zantac Cool Mint tablets that the laboratory received from GSK, BI, and Sanofi. Najafi Report at 62, 64. These drug products had been "retained, unsold or returned" to the manufacturers. *Id.* at 64. Before shipping the products to Emery Pharma, the manufacturers stored the products at a variety of storage facilities around the world under "controlled, monitored or ambient" temperature and humidity conditions. *Id.* at 63-64. "Many" of the products had three-year expiration dates. *Id.* at 63. Of the

[38] To the extent that the Plaintiffs argue that Dr. Najafi was precluded from publishing because of various court orders in this MDL, *see* DE 780, 4272, 4485, 4679, the Plaintiffs never moved for relief from those orders.

254 products that Emery Pharma tested during the baseline testing, 166 were unexpired at the time of the testing, and 88 were expired. *Id.* Dr. Najafi reports that the baseline testing revealed a range from 11.7 ng to 14,991.6 ng of NDMA per 150 mg dose of ranitidine. *Id.* at 64. The mean level of NDMA in the unexpired products was 1,096.6 ng per 150 mg dose of ranitidine. *Id.* The mean level of NDMA in the expired products was 2,222.2 ng per 150 mg dose of ranitidine. *Id.* Dr. Najafi reports that only 5 of the products tested revealed levels of NDMA lower than the FDA's acceptable NDMA daily intake level of 96 ng. *Id.* at 63.

Emery Pharma also evaluated the NDMA content of ranitidine API. The API used for the testing had been manufactured between 2010 and 2019 and, before being shipped to Emery Pharma, was stored under "temperature-controlled conditions and humidity conditions that were monitored, ambient or not controlled." *Id.* at 65. Dr. Najafi reports that testing the API revealed a range from 57.9 ng to 6,671.4 ng of NDMA per 150 mg dose of ranitidine. *Id.*

Courts apply the "substantial similarity" test to evaluate the admissibility of an out-of-court experiment intended to recreate an event or incident. *Sorrels v. NCL (Bahamas) Ltd.*, 796 F.3d 1275, 1284 (11th Cir. 2015); *see also United States v. Norris*, 217 F.3d 262, 270 (5th Cir. 2000) (referring to the substantial similarity test as a standard that courts of appeals "have consistently employed" when considering the admissibility of out-of-court experiments). "As a general rule, the district court has wide discretion to admit evidence of experiments conducted under substantially similar conditions." *Barnes v. Gen. Motors Corp.*, 547 F.2d 275, 277 (5th Cir. 1977); *see Nelson v. Freightliner, LLC*, 154 F. App'x 98, 113 (11th Cir. 2005) (applying the substantial similarity test on appeal to evaluate whether a district court abused its discretion by admitting evidence of carbon monoxide emissions testing); *United States v. Gaskell*, 985 F.2d 1056, 1060-61

(11th Cir. 1993) (applying the substantial similarity test on appeal to evaluate whether a district court abused its discretion by admitting a demonstration of shaken baby syndrome).

For an experiment to be admissible, "it is not required that all the conditions shall be precisely reproduced, but they must be so nearly the same in substantial particulars as to afford a fair comparison in respect to the particular issue to which the test is directed." *Barnes*, 547 F.2d at 277 (quoting *Ill. Cent. Gulf R. Co. v. Ishee*, 317 So. 2d 923, 926 (Miss. 1975)). The party offering the out-of-court experiment into evidence bears the burden "to lay a proper foundation demonstrating a similarity of circumstances and conditions." *Id.* At the *Daubert* stage of litigation, a court may apply the substantial similarity test as part of its evaluation of the reliability and relevance of an expert opinion that is based on an out-of-court experiment. *See Norris*, 217 F.3d at 270 ("By making a finding of 'substantial similarity,' the district court effectively conducted a *Daubert* inquiry by ensuring that the evidence was relevant and reliable, despite not expressly addressing the four non-exclusive factors listed in *Daubert* . . . ."); *cf. McDowell*, 392 F.3d at 1298-99 (explaining that scientific expert testimony meets the relevance prong of a *Daubert* analysis if it "has a justified scientific relationship to the pertinent facts" and "logically advances a material aspect of the case" (citation omitted)).

i. Parties' Arguments

The Defendants challenge the admissibility of the results of Emery Pharma's baseline testing on several grounds. The Defendants assert that the levels of NDMA that Emery Pharma detected during the baseline testing far exceed both the NDMA levels that regulatory agencies have detected in ranitidine and the NDMA levels that the laboratory itself detected during its testing for its Citizen Petition. DE 5698 at 11, 19, 24; DE 5956 at 6, 14-15. They assert that the large discrepancy between the results of Emery Pharma's baseline testing and the levels of NDMA

that have otherwise been detected in ranitidine casts doubt on the validity of the laboratory's testing methods and its results. DE 5698 at 11; *see* DE 5956 at 14.

The Plaintiffs respond that all of the Defendants' criticisms of the baseline testing go to the weight of the test results and not to their admissibility. DE 5914 at 34-35. They also note that Emery Pharma could not obtain samples for testing from the consumer market, and instead obtained the products from some of the Defendants years after ranitidine had been withdrawn from the market, because ranitidine has been withdrawn from the market. *Id.* at 34. But the samples that Emery Pharma tested were bioequivalent to the ranitidine that consumers ingested, and therefore the results of the baseline testing are helpful to the resolution of facts at issue in this litigation. *Id.* at 35-36.

ii. Analysis

The NDMA levels that the laboratory detected do not, in and of themselves, justify an exclusion of the baseline testing results. Nor does the fact that those NDMA levels may exceed the results of ranitidine testing by other scientists justify an exclusion of the baseline testing results.[39] The focus of a *Daubert* inquiry "must be solely on principles and methodology, not on the conclusions that they generate." *Daubert*, 509 U.S. at 595; *see also McDowell*, 392 F.3d at 1298 (explaining that "a court should meticulously focus on the expert's principles and methodology, and not on the conclusions that they generate"). However, "conclusions and methodology are not entirely distinct from one another." *Joiner*, 522 U.S. at 146. The levels of NDMA that Emery Pharma detected in ranitidine demonstrate a need for the Court to scrutinize

[39] As an example of the discrepancy between the results of Emery Pharma's baseline testing and the results of ranitidine testing by regulatory agencies, the Plaintiffs acknowledge that the *highest* level of NDMA that the FDA's testing has revealed in a 150 mg dose of ranitidine is around 445 or 465 ng. Defendant's Sept. 22 *Daubert* Hearing Tr. at 176. The *mean* level of NDMA that Emery Pharma's baseline testing detected in unexpired ranitidine products was 1,096.6 ng per 150 mg dose of ranitidine. Najafi Report at 64.

the laboratory's methods. *See Lust ex rel. Lust v. Merrell Dow Pharms., Inc.*, 89 F.3d 594, 598 (9th Cir. 1996) ("When a scientist claims to rely on a method practiced by most scientists, yet presents conclusions that are shared by no other scientist, the district court should be wary that the method has not been faithfully applied.").

The fact that Emery Pharma tested non-market ranitidine products also is not itself a basis to exclude the results. By the time the laboratory conducted its baseline testing, ranitidine products had been withdrawn from the consumer market. Consequently, the laboratory conducted testing on products that it received from some of the Defendants. These products were those that the manufacturers retained, that had gone unsold, or that were returned. Najafi Report at 64.

As for ranitidine products that never reached the consumer market because the Defendants retained them or otherwise did not sell them, the Court presumes that the Defendants complied with federal storage requirements while storing those products. Therefore, the products that the Defendants sent to Emery Pharma for testing were presumably stored under substantially similar temperature conditions as the temperature conditions required for a drug product that does proceed through the supply chain. This fact enables one to make a fair comparison of the NDMA levels in the tested products to the NDMA levels in the products that consumers ingested. *See Barnes*, 547 F.2d at 277 (explaining that, for an out-of-court experiment to be admissible, "it is not required that all the conditions shall be precisely reproduced, but they must be so nearly the same in substantial particulars as to afford a fair comparison in respect to the particular issue to which the test is directed" (quoting *Ishee*, 317 So. 2d at 926)).

As for the tested ranitidine products that Dr. Najafi describes as having been "returned," *see* Najafi Report at 64, the Court understands this to describe products returned to the Defendants after ranitidine was withdrawn from the consumer market, meaning that the products potentially

proceeded through the supply chain twice. That these products may have gone through the supply chain twice does not render them substantially dissimilar to the products that reached consumers. One may make a fair comparison of the NDMA levels in the returned products to the NDMA levels in the products that consumers ingested. *See Barnes*, 547 F.2d at 277.

Further, the Court does not exclude any expert's opinion based upon the results of Emery Pharma's baseline testing of ranitidine products solely because those products were expired or near expiration. At this stage of the litigation, the Court accepts as plausible the proposition that some consumers may have continued to ingest ranitidine after its labeled expiration date and that the laboratory's testing of expired products could be helpful to resolving the question of those consumers' NDMA exposure.[40]

The Court now addresses Emery Pharma's baseline testing of ranitidine API. The Plaintiffs did not respond in their briefing to the Defendants' specific argument concerning the laboratory's testing of API: that the testing does not fit the facts of this case because consumers do not ingest API and because a finished drug product provides a greater degree of protection from drug degradation than does API that has not been processed into a finished product. *See* DE 5698 at 52-53. The Plaintiffs have forfeited any response to that argument. *See Hollis v. Miami-Dade Cnty.*, No. 20-CV-21930, 2022 WL 4124300, at *7 (S.D. Fla. Aug. 10, 2022) ("It is well settled that a party who fails to respond to an argument in her response necessarily forfeits the point."), *report and recommendation adopted at* 2002 WL 4119753 (S.D. Fla. Sept. 9, 2022).

Even if the Plaintiffs had not forfeited a response to the Defendants' argument concerning the fit of API testing, the Plaintiffs have not carried their burden to show that the results of Emery

[40] Emery Pharma also used expired ranitidine products during some of its other studies, such as during the simulated consumer experience testing that the Court describes below. The Court similarly does not exclude the results of this testing solely on the basis of the age of the products.

Pharma's API testing fit the facts of this case. Dr. Najafi does not maintain that consumers ingest API that has not been processed into a finished drug product. He asserts in his rebuttal report, however, that Emery Pharma "demonstrated that the drug product making process does not influence NDMA levels." Najafi First Rebuttal Report at 224. Dr. Najafi does not expound on this demonstration, so the Court asked the Plaintiffs during oral argument where in Dr. Najafi's reports the Court may locate such a demonstration. Defendants' Sept. 22 *Daubert* Hearing Tr. at 177-78. The Plaintiffs pointed to paragraphs 262 through 264 of Dr. Najafi's expert report. *Id.* at 178.

Paragraphs 262 through 264 of Dr. Najafi's expert report are part of a description of a study whereby Emery Pharma manufactured its own ranitidine tablets using ranitidine API, stored those tablets under the conditions of one of five simulated climatic zones for four weeks, and measured the tablets' NDMA content at zero-, two-, and four-week timepoints.[41] Najafi Report at 125-29. Dr. Najafi reports that the laboratory-manufactured tablets "progressively accumulated NDMA across all tested climatic zone conditions within a period of 2 to 4 weeks." *Id.* at 129. The Court has compared this study to an Emery Pharma study whereby the laboratory stored API under the conditions of one of five simulated climatic zones for four weeks and measured the NDMA content of the API at zero-, two-, and four-week timepoints. *Id.* at 129-33.

Dr. Najafi's expert report reflects that only one batch of API—GSK Jurong API batch K280417—was used during both the study with laboratory-manufactured tablets and the study of the API. *Id.* at 126, 130. Thus, to evaluate whether Dr. Najafi has supported his conclusion that "the drug product making process does not influence NDMA levels," the Court looks to the levels

[41] The Court discusses these five zones and what their temperature and humidity conditions are intended to simulate in greater detail below. The temperature and humidity conditions of the five zones are as follows: zone I at 21 °C/69.8 °F and 45% relative humidity ("RH"); zone II at 25 °C/77 °F and 60% RH; zone III at 30 °C/86 °F and 35% RH; zone IVa at 30 °C/86 °F and 65% RH; and a fifth "Accelerated Ambient" zone at 40 °C/104 °F and 75% RH. RH is the amount of water vapor in the air at a given temperature compared to the total amount of water vapor that the air can hold at that temperature.

of NDMA that Dr. Najafi has reported for this single API batch.[42] A comparison of the NDMA levels for batch K280417 from the study with laboratory-manufactured tablets and the NDMA levels for batch K280417 from the study with the API reveals that those levels are not the same. *See id.* at 127-33. The batch K280417 API accumulated more NDMA under almost all of the zone conditions than did the tablets manufactured with batch K280417 API.[43]

Dr. Najafi has not demonstrated that tablets manufactured with a batch of API accumulate NDMA at the same rate as does the batch of API itself. And, because consumers do not ingest ranitidine API not manufactured into a finished drug product, he has not shown how the results of Emery Pharma's baseline testing of ranitidine API fit this case. *See Allison*, 184 F.3d at 1312 (explaining that, to be relevant to or "fit" the case, "evidence must have a valid scientific connection to the disputed facts in the case").

f. **Simulated Consumer Experience Testing**

Emery Pharma conducted various tests that Dr. Najafi refers to collectively as the "simulated consumer experience testing." Najafi Report at 115. Emery Pharma conducted these tests to simulate the amount of NDMA that might form in ranitidine from typical, routine conditions. First, Emery Pharma performed tests using nine Sanofi-manufactured ranitidine products with expiration dates between April 2020 and July 2022, by storing the products under temperature and humidity conditions intended to simulate those found in a car or a bathroom. *Id.*

[42] The Court considers unreliable a methodology that compares the levels of NDMA measured among different batches of API, given Dr. Najafi's position that "no two ranitidine batches have behaved identically when exposed to stress/stability conditions" and "our stability profiles across many lots and batches indicate that [NDMA formation] is highly dependent on the product itself." Najafi First Rebuttal Report at 13, 17.

[43] The only instance where Dr. Najafi reports a higher level of NDMA for a tablet manufactured with API batch K280417 than for the API itself is at the four-week timepoint under the "Accelerated Ambient" zone conditions (40 °C/104 °F and 75% RH). Dr. Najafi has theorized that NDMA eventually begins to degrade, providing a possible explanation for why the level of NDMA in the API would be lower in this instance than the level of NDMA in the laboratory-manufactured tablet. *See* DE 5698-11 at 18 ("We theorize that given the reactive nature of NDMA, rate of degradation of NDMA eventually surpasses the rate of formation which is responsible for the decrease.").

at 117. Emery Pharma did not perform any study during which the laboratory stored ranitidine in an actual car or an actual bathroom. Najafi Dep. at 230 ("We have not tested Zantac pills in a—anybody's car."); *id* at 232 ("We have not conducted a study in a real-world bathroom."). Rather, the laboratory placed ranitidine tablets in an instrument called a Darwin chamber, which is a scientific instrument that is able to produce precise temperature and humidity conditions.

One of Emery Pharma's studies was meant to simulate temperatures that could be found in a car. First, Emery Pharma simulated temperatures in a car parked in the shade by beginning with ranitidine tablets stored at an "ambient temperature" of 25 °C/77 °F, storing them for 2 hours at 40 °C/104 °F, and then storing them for an additional 2 hours at the ambient temperature. *Id.* at 116; DE 5698-10 at 147. Second, Emery Pharma simulated temperatures in a car parked in the sun by beginning with ranitidine tablets stored at the ambient temperature of 25 °C/77 °F, storing them for 2 hours at 75 °C/167 °F, storing them for 2 hours at 50 °C/122 °F, and then storing them for 4 hours at the ambient temperature. DE 5698-10 at 147. Dr. Najafi reports that Emery Pharma measured the NDMA content of tablets after they had undergone 0 of these temperature cycles, 15 cycles, 30 cycles, and 50 cycles. Najafi Report at 117-18.

Emery Pharma also conducted a study meant to simulate the temperature and humidity conditions in a bathroom. For this test, ranitidine tablets initially were stored under "ambient bathroom conditions" of 25 °C/77 °F and 40% relative humidity ("RH"), were stored for 30 minutes under 40 °C/104 °F and 100% RH, and then "were allowed to equilibrate back to ambient conditions." Najafi Report at 116; DE 5698-10 at 147. Dr. Najafi reports that Emery Pharma

measured the NDMA content of tablets after they had undergone 0 of these temperature-humidity cycles, 15 cycles, 30 cycles, and 50 cycles.[44] Najafi Report at 118.

Dr. Najafi provides some of the NDMA levels that Emery Pharma measured during the car and bathroom simulations in his expert report. *See id.* at 117-18. He states that "NDMA continued to form over 50 cycles under simulated storage for a car (shade or sun) or bathroom medicine cabinet" and that these results "demonstrate that a significant amount of NDMA, in addition to any baseline NDMA content, continue[s] to form after a consumer opens the bottle depending on the storage conditions." *Id.* at 119. Dr. Najafi opines that "considering only baseline NDMA amounts in the tablets when evaluating a patient's exposure to NDMA from ranitidine may not be capturing their total NDMA exposure depending on how that patient stored their medicine." *Id.*

Finally, Emery Pharma performed a study that Dr. Najafi asserts "simulated climatic zones . . . to resemble the temperature and humidity conditions across the United States." *Id.* at 116. The laboratory conducted this study with five ranitidine products manufactured by Sanofi or GSK with expiration dates between June 2020 and June 2022. *Id.* at 122. The products were stored under temperature and humidity conditions meant to simulate five climatic zones: zone I at 21 °C/69.8 °F and 45% RH; zone II at 25 °C/77 °F and 60% RH; zone III at 30 °C/86 °F and 35% RH; zone IVa at 30 °C/86 °F and 65% RH; and a fifth zone that Dr. Najafi refers to as "Accelerated Ambient" at 40 °C/104 °F and 75% RH. *Id.* at 122; DE 5698-10 at 147. Dr. Najafi reports that Emery Pharma measured the NDMA content of ranitidine tablets that had been stored under the temperature and humidity conditions of one of these five climatic zones for zero, two, four, and eight weeks. He provides the NDMA levels that the laboratory detected in his expert report. *See id.* at 123-25. Dr.

[44] The record reflects that, for both the car and the bathroom simulations, tablets were also tested for NDMA after six cycles. *See* DE 5698-4 at 33, 42; DE 5698-11 at 23; Najafi Dep. Ex. 9. Dr. Najafi does not include in his report the NDMA levels after six cycles.

Najafi states that "all samples tested, regardless of starting NDMA level, formed more NDMA when stored in each of the five tested climatic zone conditions." *Id.* at 125.

i. Parties' Arguments

The Defendants challenge the admissibility of the results of Emery Pharma's simulated consumer experience testing. The Defendants point out that the laboratory did not conduct any study with an actual car or an actual bathroom. DE 5698 at 20, 30, 32. Emery Pharma's simulations of climatic zones did not follow methods that have been established for testing drug products within various climatic zones because the laboratory used a different container than the one that ranitidine came in, failed to include an induction seal, and included more headspace than would be in a bottle of ranitidine.[45] *Id.* at 34.

The Plaintiffs respond that Emery Pharma's car and bathroom simulations replicated temperature and humidity conditions to which consumers' ranitidine products logically could have been subject. DE 5914 at 36-38. Emery Pharma's simulations of climatic zones were based on parameters for drug stability testing that are modeled on temperature and humidity conditions across the United States. *Id.* at 38. The laboratory used a tablet bottle that is designed for pharmaceutical use and similar to the packaging for ranitidine. *Id.*

ii. Analysis

The Court begins by discussing the study in which Emery Pharma sought to simulate the storage of ranitidine in a car parked in the sun and in the shade. The Court then discusses the laboratory's study to simulate the storage of ranitidine in a bathroom. Then, the Court addresses the study to simulate ranitidine stored in various climatic zones.

[45] An induction seal is the material that is sealed to the mouth of a pill bottle under the bottle's cap. Headspace refers to the amount of air in a container.

Car Simulations

Dr. Najafi maintains that Emery Pharma modeled all of its studies on other scientific studies. Najafi Dep. at 193 (testifying that "everything we've done, you know, at Emery has been modeled after some prior scientific studies"); *id.* at 331 ("Everything we've done is rooted, is anchored in a peer-reviewed publication . . . ."). According to the laboratory's protocol for its simulated consumer experience testing, which Dr. Najafi attaches to his expert report, the car simulations were modeled on a research paper: Jennifer K. Vanos et al., *Evaluating the Impact of Solar Radiation on Pediatric Heat Balance Within Enclosed, Hot Vehicles*, 5 Temperature 276 (2018). *See* DE 5698-10 at 146; *see also* Najafi Dep. at 226 ("Our study is really based on a peer-reviewed publication related to temperatures that a car can—you know, essentially [under]go during summer."). The Court therefore examines this research paper.

The authors of the Vanos research paper examined the thermal environment to which a child left unattended in a car during a summer month could be subject and determined how that environment would influence the child's core body temperature. Vanos et al., *supra*, at 276-77. The authors conducted their experiment in Tempe, Arizona between June 25 and July 11, 2014. *Id.* at 277. To conduct the experiment, 3 vehicles were parked in the sun for a "heating period" of approximately 60 minutes. *Id.* at 276-77. After the heating period, the authors measured the cars' cabin temperatures and the surface temperatures of the cars' dashboards, steering wheels, and seats. *Id.* at 277-78. The authors then ran the air conditioning in the cars to cool the cabin temperatures to the cooler of the outdoor air temperature or 29.4 °C/85 °F. *Id.* at 277. This heating-and-cooling cycle was repeated three to five times throughout a day. *Id.* According to the authors, the average cabin temperature in these sun-exposed cars after 60 minutes was 46.7 °C/116 °F. *Id.* at 282. The average dashboard, steering wheel, and seat temperatures in the sun-exposed cars after

60 minutes were 68.9 °C/156 °F, 53.3 °C/128 °F, and 50.6 °C/123 °F, respectively. *Id.* Addressing the differences in these three surface temperatures, the authors explained, "This variability among the three surfaces is expected given the dashboard is more directly exposed to solar radiation." *Id.*

In addition to studying the temperatures of cars parked in the sun, three cars were also parked in the shade under a solar canopy for identical heating-and-cooling cycles. *Id.* at 277. According to the authors, the average cabin temperature in these shade cars after 60 minutes was 38.3 °C/111 °F. *Id.* at 282. The average dashboard, steering wheel, and seat temperatures in the shade cars after 60 minutes were 47.8 °C/118 °F, 41.7 °C/107 °F, and 41.1 °C/106 °F, respectively. *Id.* Using their temperature measurements from the sun-exposed and shade cars, the authors performed calculations to estimate the impact that the temperatures would have on the core body temperature of a hypothetical two-year-old boy left unattended in the cars.

The Vanos study examined the impact that car temperatures could have on a toddler's body temperature. The study had nothing to do with the impact of temperature on a drug product. The study had nothing to do with drugs or drug stability at all. Under the *Daubert* factors, Dr. Najafi has not demonstrated that Vanos provides a reliable methodology for studying the impact of temperature on a drug product. Dr. Najafi has not shown that any scientist outside of Emery Pharma has tested, reviewed, or validated an experimental design for studying drug stability that is modeled on the Vanos study or the results of that study. Dr. Najafi has not shown that reliance on Vanos to conduct a drug stability study has been accepted in the scientific community. Emery Pharma's study modeled on Vanos has not been peer reviewed or published, and the results of the laboratory's study have no known rates of error.

Even if modeling an experimental design for a drug stability study on Vanos were a reliable methodology, Dr. Najafi has not demonstrated that Emery Pharma's car simulations actually

comported with such a model. First, Emery Pharma did not follow the "heating period" used during the Vanos study. The authors in Vanos parked the cars in the sun or the shade for approximately 60 minutes, simulating a shopping trip where a small child is left in the car. Emery Pharma's car simulations instead stored ranitidine tablets at given temperatures for at least two hours.

Second, Emery Pharma did not simulate the way in which temperatures rise in real cars, such as the cars used during the Vanos study. The temperatures in the Vanos cars rose over the course of the 60-minute heating period from the "cool" temperature (the cooler of the outdoor air temperature or 29.4 °C/85 °F) at minute 0 to the higher temperatures eventually measured around minute 60. It is common sense that the temperature within the enclosed interior of a car parked outside in a hot climate will progressively rise. Yet Emery Pharma's study did not simulate a progressively rising car temperature. Rather than progressively raising the temperatures to which ranitidine tablets were subject, the laboratory transferred the tablets from the "ambient temperature" (25 °C/77 °F) to the highest temperatures used for the study (40 °C/104 °F to simulate a car parked in the shade and 75 °C/167 °F to simulate a car parked in the sun) and back again to the ambient temperature. Dr. Najafi provides no authority to show that temperatures change in a real car in such a manner.

Third, Dr. Najafi has not explained how the results of the Vanos study justify the highest temperature (75 °C/167 °F) that Emery Pharma used to simulate ranitidine stored in a car parked in the sun. The Vanos authors report that the average cabin temperature in the sun-exposed cars after 60 minutes was 46.7 °C/116 °F, with a temperature range between 40.2 and 52.2 °C. *Id.* at 280, 282. The authors further report that the average seat temperature in the sun-exposed cars after 60 minutes was 50.6 °C/123 °F, with a temperature range between 45.6 and 63.3 °C. *Id.* Emery

Pharma exposed ranitidine tablets to a significantly higher temperature than the cabin and seat temperatures measured in Vanos. While the steering wheel surface temperatures measured in Vanos reached up to 78.9 °C/174 °F, Dr. Najafi does not contend that ranitidine tablets could be stored on a car's steering wheel to justify simulating storage under such a temperature.

Dr. Najafi does not appear to rely on the cabin, seat, or steering wheel temperatures observed in Vanos to substantiate the highest temperature that Emery Pharma used to simulate ranitidine stored in a car parked in the sun. According to Dr. Najafi, utilizing a temperature approximating a car cabin temperature would be unjustified because a ranitidine tablet would never be stored in a car suspended in midair. Najafi First Rebuttal Report at 14 ("A ranitidine pill being carried in a car will not be magically suspended mid-air to justify considering the cabin air temperatures"). Dr. Najafi defends the highest temperature that Emery Pharma used for its simulation as instead being comparable to the most extreme temperatures measured in Vanos: the dashboard temperatures. *See id.* The Vanos authors report that the dashboard temperatures ranged between 46.7 and 85 °C in the sun-exposed cars, with an average temperature of 68.9 °C/156 °F. Vanos et al., *supra*, at 280, 282.

Dr. Najafi's justification for simulating ranitidine storage under a temperature approximating the dashboard temperatures measured in Vanos is based on presumptions for which he has offered no support. As an initial matter, he presumes, without support, that consumers stored ranitidine in car glove compartments. Najafi First Rebuttal Report at 14 (referring to the glove compartment as "a likely storage location" for ranitidine).

More problematic, however, is Dr. Najafi's presumption that car glove compartments reach temperatures that are comparable to the car dashboard temperatures measured in Vanos. The only statement that Dr. Najafi makes in his reports that could be construed as offering support for such

a presumption is that a car's glove compartment is "in contact" with a dashboard. *See id.* (stating that "the glove compartment, a likely storage location is directly in contact to the dashboard"). The Vanos authors explained why a dashboard temperature would exceed temperatures found elsewhere in a car by pointing out that "the dashboard is more directly exposed to solar radiation." Vanos et al., *supra*, at 282. Dr. Najafi does not contend that the inside of a glove compartment is similarly "directly exposed to solar radiation," and he does not otherwise explain the leap between the temperature of a dashboard directly in the sun and the temperature of the interior of a glove compartment.

Instead of attempting to further explain why Emery Pharma utilized temperatures comparable to those discovered on sun-exposed dashboards, Dr. Najafi points to two additional sources in his rebuttal report that, according to him, support the laboratory's use of 75 °C/167 °F when simulating ranitidine stored in a car parked in the sun. *See* Najafi First Rebuttal Report at 15. Dr. Najafi states that one of the sources—a 2009 research paper on car temperatures in Georgia—supports a proposition that car cabin temperatures can reach between 41 and 76 °C (106 to 169 °F) depending on the time of year and weather conditions, while the second source—a 1979 report on common carrier shipping conditions—supports a proposition that cargo surface temperatures in a common carrier truck can reach 71 °C/160 °F. *Id.*

Dr. Najafi does not contend that Emery Pharma based its experimental design on either of these additional sources, and the laboratory's protocol for the car simulations indicates that the simulations were instead modeled on Vanos. *See* DE 5698-10 at 146. In any event, even if these sources provide support for a proposition that car cabin temperatures are theoretically capable of reaching 75 °C/167 °F (the highest temperature that Emery Pharma used during its car simulations), for the same reasons as with the Vanos study and applying the same *Daubert* factors,

Dr. Najafi has not demonstrated that these other sources provide a reliable methodology for studying the impact of temperature on a drug product.

Finally, Dr. Najafi has not shown that Emery Pharma's car simulations, whether loosely based on Vanos or not, fit the facts of this case. Dr. Najafi has not demonstrated that the laboratory's car simulations bear a substantial similarity to conditions under which any consumer's ranitidine product would have been stored. *See Barnes*, 547 F.2d at 277 (explaining that, for an out-of-court experiment to be admissible, the conditions of the experiment "must be so nearly the same in substantial particulars as to afford a fair comparison in respect to the particular issue to which the test is directed" (citation omitted)). Emery Pharma did not study NDMA levels in ranitidine after storing it in an actual car, but rather stored ranitidine in Darwin chambers capable of producing certain temperatures. And Dr. Najafi has not explained how transferring tablets between one temperature and another replicates temperature changes as they occur in the interior of a real car. Moreover, to the extent that Emery Pharma did not replicate the way in which temperatures change in a real car, Dr. Najafi has not explained how the laboratory's unrealistic temperature changes may have impacted the formation of NDMA in the ranitidine tablets studied or how the results of the laboratory's simulations may be extrapolated so as to be indicative of the levels of NDMA in tablets stored in consumers' cars.[46] In conclusion, Dr. Najafi has not demonstrated that the levels of NDMA that Emery Pharma measured following its car simulations were achieved through a reliable methodology or that those results fit this case.

Bathroom Simulation

According to Emery Pharma's protocol for the simulated consumer experience testing attached to Dr. Najafi's expert report, the bathroom simulation was modeled on a report from a

[46] For a detailed discussion of extrapolation, see Section V(B)(2)(b)(ii), *infra*.

study: Y. Aizawa et al., *Thermal Environment and Moisture Production in the Bathroom* (2006). *See* DE 5698 Ex. 20; DE 5698-10 at 146. The Court therefore examines this study.

The Aizawa study examined the humidity and thermal environment of Japanese bathrooms during showering and bathing to determine how using ventilation in a bathroom influences that environment. DE 5698 Ex. 20 at 1, 6. The authors of the study conducted an experiment in a bathroom with the following dimensions: 1150 millimeters wide, 1600 mm long, and 2000 mm high. *Id.* at 1. Converting these measurements to inches, the bathroom's dimensions were approximately 45 inches wide by 63 inches long by 79 inches high. The bathroom contained a bathtub which had a cover. The bathroom was connected through a folding door to a "changing room" that was 1200 mm (47 inches) wide, 1200 mm (47 inches) long, and 2300 mm (91 inches) high. *Id.* The authors simulated a summer climate by keeping the bathroom at 28 °C/82 °F and 75% RH before showering or bathing occurred. *Id.* at 3. The authors used 20 °C/68 °F and 50% RH to simulate a "mid-season" climate and used 10 °C/50 °F and 30% RH to simulate a winter climate. *Id.* The experiment was conducted by having participants shower or bathe in the bathroom. *Id.* at 2. Some participants used ventilation while they showered or bathed, while others did not. *Id.*

The authors measured the temperatures and levels of humidity in the bathroom and the changing room after these showers and baths. The authors discovered, "During bathing, the relative humidity of the bathroom reached 100% right after opening the cover for the bath tub and letting the shower run, regardless [of] the operation [of] the ventilation and the season." *Id.* Showering and bathing caused the temperatures in the rooms to increase, with the temperature increase being more significant if no ventilation was used. *Id.* at 3-4. The temperatures and

humidity levels gradually decreased after the bathing and showering, with this decrease occurring more quickly with the use of ventilation. *Id.* at 4.

The Aizawa study has nothing to do with drug stability or the effect that a bathroom environment could have on a drug product. Under the *Daubert* factors, Dr. Najafi has not demonstrated that Aizawa provides a reliable methodology for studying the impact of heat and humidity on a drug product. Dr. Najafi has not shown that any scientist outside of Emery Pharma has tested, reviewed, or validated an experimental design for studying drug stability that is modeled on Aizawa. Dr. Najafi has not shown that reliance on Aizawa to conduct a drug stability study has been accepted in any scientific community. Emery Pharma's study modeled on Aizawa has not been peer reviewed or published, and the results of the laboratory's study have no known rates of error.

Even if modeling an experimental design for a drug stability study on Aizawa were a reliable methodology, Dr. Najafi has not demonstrated that Emery Pharma's bathroom simulation comported with such a model. Dr. Najafi reports, "The Aizawa study found bathrooms reaching maximums around 37°C/100% RH, and that the conditions in the 'changing room' (where a medicine cabinet would presumably be located) reached 25°C/85% RH for about five minutes when starting at about room temperature." Najafi First Rebuttal Report at 16. Dr. Najafi testified that it is reasonable to believe that consumers stored ranitidine in bathroom medicine cabinets. Najafi Dep. at 177 (asserting that "millions of people keep their pills in their medicine cabinet"). Dr. Najafi does not explain why, if consumers stored ranitidine in their medicine cabinets, and if a medicine cabinet would be located in an area approximating the Aizawa changing room, Emery Pharma's bathroom simulation nevertheless utilized temperature and humidity conditions (40

°C/104 °F and 100% RH) more extreme than the conditions observed in the changing room and instead more closely approximating the conditions observed in the bathroom.

The conditions to which Emery Pharma subjected ranitidine tablets diverged from those observed in Aizawa even further. The laboratory placed ranitidine tablets in 40 °C/104 °F and 100% RH for 30 minutes, longer than the durations of the participants' showers or baths in Aizawa. And, by Dr. Najafi's own admission, the 40 °C/104 °F temperature that Emery Pharma utilized was more extreme than the highest temperature measured in the Aizawa bathroom. Najafi First Rebuttal Report at 16 (stating that the temperature in the Aizawa study "was indeed measured at 3 °C lower than our study"). Dr. Najafi maintains that the impact of those "few degrees" on Emery Pharma's test results would be "negligible." *Id.* ("The impact of a few degrees in temperature is negligible considering the abundance of data Emery Pharma has provided demonstrating the impact of temperature at both higher and lower conditions than 37° C as seen in the car in shade/sun studies as well as the zone stability studies."). But Dr. Najafi does not purport to have conducted any studies where the storage conditions for ranitidine were varied by a few degrees at 100% RH to confirm the impact that those few degrees might have on NDMA formation in ranitidine. He has not demonstrated that his theory—that diverging from the conditions observed in Aizawa by a few degrees had a negligible impact on NDMA formation—is more than speculation. *See Chapman*, 766 F.3d at 1306 (explaining that a court performing a *Daubert* analysis must determine whether the proffered expert is offering evidence that is genuinely scientific or unscientific speculation).

Furthermore, as with the car simulations, Emery Pharma did not simulate the way in which temperatures and levels of humidity rise in a real bathroom. It is common sense that the temperatures and humidity levels progressively rise as the water for a shower or bath runs. Yet

Emery Pharma's study did not simulate progressively rising temperatures or humidity conditions. Rather, the laboratory transferred ranitidine tablets from "ambient bathroom conditions" (25 °C/77 °F and 40% RH) to the more extreme conditions (40 °C/104 °F and 100% RH) and back again to the ambient conditions. Dr. Najafi provides no authority to show that temperature or humidity conditions change in a real bathroom in this manner. To the extent that Emery Pharma did not replicate the way in which conditions change in a real bathroom, Dr. Najafi has not explained how the unrealistic changes may have impacted the formation of NDMA in the ranitidine tablets studied or how the results of the laboratory's simulation may be extrapolated so as to be indicative of the levels of NDMA in tablets stored in consumers' bathrooms.

Dr. Najafi also has not shown how the conditions observed in the Aizawa bathroom, on which Emery Pharma loosely based its bathroom simulation, fit the facts of this case. The design of the Aizawa study represented a Japanese bathroom. The bathroom used for the study was rather unique. Based on the dimensions that the study's authors report, the bathroom was quite small. Logically, the compactness of a bathroom would impact the extent and rate at which temperature and humidity would rise during a shower or bath. The bathtub utilized in Aizawa had a cover, such that the bathtub could be filled with water, covered, and then uncovered for a person to enter the bathtub. Logically, a cover would impact the level of humidity in a bathroom. Dr. Najafi has not explained how this Japanese bathroom compares to the bathrooms in which consumers in the United States may have stored ranitidine products.

In sum, Dr. Najafi has not demonstrated that the levels of NDMA that Emery Pharma measured through its bathroom simulation were achieved through a reliable methodology or that those results fit this case.

Simulated Climatic Zones

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH") is an assembly of regulatory authorities and members of the pharmaceutical industry seeking to ensure safe, effective, and high-quality medicines.[47] The ICH has divided climates throughout the world into four climatic zones (zones I through IV) for the purpose of studying drug stability. *See* ICH, *ICH Harmonised Tripartite Guideline: Stability Testing of New Drug Substances and Products Q1A(R2)*, at 1 (2003) [hereinafter *ICH Harmonised Tripartite Guideline*], https://database.ich.org/sites/default/files/Q1A%28R2%29%20Guideline.pdf; U.S. Dep't of Health & Hum. Servs., FDA, Ctr. For Drug Evaluation & Rsch., Ctr. For Biologics Evaluation & Rsch., *Guidance for Industry: Q1A(R2) Stability Testing of New Drug Substances and Products* 2 (2003), https://www.fda.gov/media/71707/download. The temperature and humidity conditions under which Emery Pharma stored ranitidine that Dr. Najafi refers to as zones I, II, III, and Iva were modeled on the ICH's four climatic zones.[48] The temperature and humidity conditions under which Emery Pharma stored ranitidine that Dr. Najafi refers to as "Accelerated Ambient" was modeled on the ICH's accelerated testing conditions.

The Defendants argue that Dr. Najafi's "Accelerated Ambient" climatic zone testing of ranitidine does not fit the facts of this MDL and, as a result, is precluded under *Daubert* because the simulated testing conditions assume that ranitidine is stored in outdoor, ambient temperatures and is exposed to outdoor, ambient relative humidity levels as well. DE 5698 at 34.[49] In response,

[47] *See generally ICH: Harmonisation for Better Health*, https://www.ich.org (last visited Oct. 20, 2022).
[48] ICH Zone IV is divided into Zone IVa, a hot and humid zone (30 °C/86 °F and 65% RH), and Zone IVb, a hot zone with even higher humidity (30 °C/86 °F and 75% RH).
[49] The Defendants raise other challenges as well, such as a challenge towards the containers that Emery Pharma used to store its test samples, but the Court's ruling is based upon the ambient outdoor humidity levels in conjunction with ambient outdoor temperatures.

the Plaintiffs emphasize that Emery Pharma's testing conditions were derived from a reputable source, the *ICH Harmonised Tripartite Guideline*. DE 5914 at 38.

The purpose of the ICH guidelines is not to design testing conditions that determine how much of an impurity may realistically form in a real-world, consumer-ingested product. Instead, the purpose of the ICH guidelines is to "provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors." *ICH Harmonised Tripartite Guideline*, *supra*, at 4. That evidence is used by regulatory authorities to determine whether a new drug should be approved for sale. *Id.* The guideline expressly recognizes that its accelerated testing parameters are "designed to increase the rate of chemical degradation or physical change of a drug substance or drug product **by using exaggerated storage conditions**" and that the data from such studies "**are not always predictive** of the physical changes." *Id.* at 13 (emphasis added).

Looking at the fit of Emery Pharma's climatic zone testing to this MDL, the ICH guideline testing conditions used a range of outdoor, ambient temperatures in conjunction with a range of outdoor, ambient relative humidity levels. The highest relative humidity was 95%, and the lowest relative humidity was 65%.[50] Putting aside whether outdoor, ambient temperatures *in isolation* are a fit for the facts of this MDL, the Court focuses on the relative humidity tested *in conjunction* with outdoor ambient temperatures.

Dr. Najafi emphasizes how important humidity was to the results of his testing: "For each temperature condition, humidity played a major role in NDMA formation from ranitidine." Najafi Report at 77. It is clear from Dr. Najafi's report that the greater the relative humidity Emery Pharma used, the greater the amount of NDMA that Emery Pharma detected. *Id.* at 78. Yet Emery

[50] Dr. Najafi's graphs include references to 60% relative humidity tests, however, the Court believes this number to be a typographical error based upon the data in Dr. Najafi's report. *E.g.,* Najafi Report at 76.

Pharma's climatic zone simulations did not test ranitidine in an indoor consumer's environment, such as an air-conditioned room with lower relative humidity, or in a shipping environment, such as the interior of a truck, or in an indoor storage environment, such as a warehouse. Dr. Najafi provides no scientific basis or evidentiary support for his assumption that the typical Plaintiff or distributor in this MDL stores ranitidine at 65% relative humidity or stores ranitidine in an outside, non-air-conditioned environment.

The Court's understanding is that a target relative humidity for an air-conditioned home in the United States is 45%,[51] and that a relative humidity of 70% or greater will result in mold growth. *Conditions that Promote Mold Growth*, N.C. Dep't Health & Hum. Servs., https://epi.dph.ncdhhs.gov/oee/mold/conditions.html (last visited Oct. 19, 2022). In any event, Dr. Najafi's conclusion, utilizing outdoor relative humidity levels in conjunction with outdoor ambient temperatures to quantify the amount of NDMA that might realistically have formed in the ranitidine that the Plaintiffs purchased, is based on an analytical leap unsupported by the evidence.

For all of the reasons set forth above, Emery Pharma's car simulations, bathroom simulations, and climatic zone simulations are inadmissible under *Daubert* as the simulations were conducted pursuant to unreliable scientific methodologies and are an improper fit to the facts of this MDL.

g. **Simulated Gastric Fluid ("SGF") Testing**

Emery Pharma conducted two types of testing—without food and with food—using SGF at a temperature of 37 °C/98.6 °F to simulate the human stomach. Najafi Report at 80. The parties focus their arguments in the briefing on the laboratory's SGF testing with food.

[51] *Temperature and Humidity Design Criteria*, IBM (Mar. 4, 2021), https://www.ibm.com/docs/en/power5?topic=preparation-temperature-humidity-design-criteria.

Dr. Najafi reports, "Emery Pharma conducted a[n] SGF food study using meats (all fully cooked): Smithfield Anytime Favorites Boneless Ham Steak Hickory Smoked ('Ham'), Oscar Mayer Center Cut Bacon ('Bacon'), Ballpark Angus Beef Franks Original ('Hotdog'), and Johnsonville 100% Premium Pork Fully-Cooked Breakfast Sausage ('Sausage')." *Id.* at 94. Emery Pharma itself did not cook or otherwise heat any of the refrigerated meat products before using them for the study. Najafi Dep. at 257 ("We have no kitchen here to cook. Everything, they come as is."). Each meat product was prepared for testing by removing it from a refrigerator and "by blending [it] for at least 60 seconds at [the] highest setting or until [it was] pulverized." DE 5698-10 at 151; Najafi Dep. at 258 ("They were kept in the refrigerator, at refrigerator temperature, and when they were ready to do the study . . . the meat was prepared . . . .").

According to the protocol for this study, one serving of a pulverized meat product and 150 mg of ranitidine that had been crushed to a powder were combined in SGF with a pH level of 1.2. DE 5698-10 at 150-51. Dr. Najafi reports that Emery Pharma followed two different designs for this study: (1) first adding the pulverized meat to the SGF and adding the crushed ranitidine 30 minutes later (which Dr. Najafi refers to as the "Meat then Zantac" design), and (2) first adding the crushed ranitidine to the SGF and adding the pulverized meat 30 minutes later (which Dr. Najafi refers to as the "Zantac then Meat" design). Najafi Report at 99; DE 5698-10 at 151. According to Dr. Najafi, these two designs "were pursued to evaluate 'real-life' scenarios of consumers taking ranitidine following or preceding a meal, respectively." Najafi Report at 94-95. As controls, Emery Pharma also tested crushed ranitidine alone in SGF, pulverized meat alone in SGF, and pulverized meat spiked with 500 ng per milliliter ("mL") of NDMA in SGF. *Id.* at 94, 102. The NDMA levels in the SGF for all five of these designs were measured at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5 and 4-hour timepoints. *Id.* at 94.

Dr. Najafi reports in tabular and graph formats the results of this study. *See id.* at 95-100. To summarize the results contained in Dr. Najafi's expert report, for the designs combining sausage and ranitidine and combining bacon and ranitidine, quantifiable levels of NDMA were detected at the 2-hour timepoint, and those levels increased through the 4-hour timepoint. *Id.* at 100-01, 103-04. For the designs combining ham and ranitidine, quantifiable levels of NDMA were detected at the 1.5-hour timepoint and increased through the 4-hour timepoint. *Id.* at 96-97. And for the designs combining hot dog and ranitidine, quantifiable levels of NDMA were detected at the 2.5-hour timepoint, and those levels were variable through the 4-hour timepoint. *Id.* at 99-100. Dr. Najafi reports that the order in which the pulverized meat and crushed ranitidine were added to the SGF—that is, the Meat then Zantac design versus the Zantac then Meat design—"did not have an effect on NDMA production."[52] *Id.* at 101.

Dr. Najafi concludes that Emery Pharma's study "provide[s] insight into the level of exposure that patients may experience when consuming ranitidine in 'real-life' scenarios," supports a conclusion that "different processed meats, when interacting with ranitidine, result in varying but significant total NDMA formation," and suggests that "the food matrix, plays an important role in NDMA formation from ranitidine." *Id.* at 101-02. Dr. Najafi reports, "Additionally, we considered several 'high-nitrate' food products, e.g., Arugula, but they did not influence NDMA formation from ranitidine." *Id.* at 104.

[52] Dr. Najafi criticizes a published, peer-reviewed, and placebo-controlled study conducted by FDA scientists wherein participants ingested either a placebo or ranitidine before consuming a meal, and then the participants' urine and blood plasma was tested for the presence of NDMA. *See* Jeffrey Florian et al., *Effect of Oral Ranitidine on Urinary Excretion of N-Nitrosodimethylamine (NDMA): A Randomized Clinical Trial*, 326 JAMA 240 (2021). According to Dr. Najafi, one of the problems with the Florian study is that the participants ingested ranitidine on an empty stomach before consuming their meals, and the study did not examine what may happen if ranitidine is taken after eating. Najafi Report at 105 ("When a patient takes Zantac to relieve symptoms, it can be taken when food is present in the stomach. Accordingly, the Florian study missed an extremely critical aspect of NDMA production from ranitidine: interaction with food."). If the result that Dr. Najafi reports about Emery Pharma's own testing—that the order in which the pulverized meat and crushed ranitidine were added to the SGF did not affect NDMA production—is valid, then it would appear immaterial that the Florian study did not examine ranitidine being ingested after eating.

Notably, all of the tests that added only crushed ranitidine to SGF or only pulverized meat to SGF revealed levels of NDMA that were below the limit of detection, which Dr. Najafi reports was under 2.5 ng per mL. *Id.* at 96-100. Dr. Najafi states that these controls show that "detectable levels of NDMA are not formed in Zantac alone" and that "none of the meat products evaluated inherently contained any detectable NDMA levels." *Id.* at 102.

i. Parties' Arguments

The Defendants maintain that the results of Emery Pharma's SGF study with food are inadmissible. They contend that the study departed from scientific models established to simulate the digestive process and failed to account for physiological conditions and reactions (that is, conditions that are found and reactions that occur within the human body). DE 5698 at 21, 37-38. Putting aside Emery Pharma's faulty SGF testing, the scientific evidence is in agreement that NDMA does not form from ranitidine endogenously. This scientific evidence includes well-conducted *in vitro* and *in vivo* studies by the FDA. *Id.* at 17, 36-37.

The Plaintiffs respond that multiple studies and sources support the proposition that NDMA can form from ranitidine endogenously.[53] DE 5914 at 39-40. *See generally* DE 5913. Emery Pharma's SGF study comports with *in vitro* methodologies that the scientific community uses to predict how a drug reacts *in vivo*. DE 5914 at 7, 21, 39-41. Numerous variables affect the conditions of a human stomach, and the Defendants' criticisms that Emery Pharma did not use the right conditions goes to the weight of the study's results rather than to their admissibility. *Id.* at 42-43.

[53] The Court discusses the topic of endogenous formation of NDMA from ranitidine in greater detail below in Section V(B).

ii. Analysis

Dr. Najafi maintains that Emery Pharma's SGF study using food "provide[s] insight into the level of [NDMA] exposure that patients may experience when consuming ranitidine in 'real-life' scenarios." Najafi Report at 102. Dr. Najafi has not demonstrated that this study provides insight that would be helpful to a jury to determine the quantities of NDMA that might form within the stomach of a ranitidine consumer.

The Plaintiffs have not carried their burden to demonstrate that the results of Emery Pharma's SGF testing can be reliably extrapolated to support the Plaintiffs' endogenous formation theory. Emery Pharma's study methodology failed to simulate the human digestion process in several ways. First, the laboratory blended meat instead of utilizing a method that scientists have developed to simulate human mastication, that is, the process by which food is ground by the teeth and broken down by saliva in the mouth to enable the food to be swallowed. *See* André Brodkorg et al., *INFOGEST Stativ In Vitro Simulation of Gastrointestinal Food Digestion*, 14 Nature Protocols 991, 991 (2019) (describing a method where food is minced, diluted with simulated salivary fluid, and incubated at 37 °C/98.6 °F to a achieve a swallowable substance with a paste-like consistency and explaining that this method was "designed to be used with standard laboratory equipment and requires limited experience").

Second, Emery Pharma did not simulate how gastric pH levels change as food enters the stomach and as the food is digested, despite scientists having developed a method to simulate the variability of gastric pH levels for *in vitro* studies of food digestion. *See* Ana-Isabel Mulet-Cabero et al., *A Standardised Semi-Dynamic* In Vitro *Digestion Method Suitable for Food – An International Consensus*, 11 Food & Function 1702, 1703 (2020) (describing a model designed to "easily be used in laboratories across the world and to a wide range of foods"); Cyrille A.M. Krul

et al., *Intragastric Formation and Modulation of N-nitrosodimethylamine in a Dynamic In Vitro Gastrointestinal Model Under Human Physiological Conditions*, 42 Food & Chem. Toxicology 51, 51 (2004). Consideration of physiological gastric pH conditions is particularly important to an attempt to quantitate NDMA exposure, as gastric pH has been shown to impact the endogenous formation of NDMA. *See, e.g.*, Krul et al., *supra*, at 61 ("It is evident that the endogenous formation of NDMA depends on many factors, including the pH in the gastric compartment . . . ."). And third, Emery Pharma did not simulate the way in which digested food gradually leaves the stomach and the stomach empties during digestion, although scientists too have developed a method to simulate gastric emptying for *in vitro* studies of food digestion. *See id.*; Mulet-Cabero et al., *supra*, at 1703.

Sources caution against drawing conclusions about the endogenous formation of NDMA from *in vitro* studies performed under nonphysiological conditions. *See, e.g.*, Zongming Gao, *In Vitro Analysis of N-nitrosodimethylamine (NDMA) Formation from Ranitidine Under Simulated Gastrointestinal Conditions*, JAMA Network Open, June 28, 2021, at 1, 7 ("[B]ecause amine nitrosation reactions, which form nitrosamines, are very dependent on the chemical environment and the presence of a suitably reactive amine group, care should be taken in ascribing observed reactivity under nonphysiologic conditions as evidence for the potential of drugs such as ranitidine to form NDMA in humans."); Krul et al., *supra*, at 61 ("It is important to investigate NDMA formation under various physiological conditions present in the human gastrointestinal tract."). Dr. Najafi has not explained how, despite Emery Pharma's failure to simulate physiological processes such as the three that the Court has identified, the results of the laboratory's SGF study can nevertheless be extrapolated to show that ranitidine forms NDMA in a human stomach. He

has not demonstrated how to bridge the analytical gap between the laboratory's study design and the human digestion process.

Furthermore, Dr. Najafi has not explained how Emery Pharma's simulation of stomach contents fits the facts of this case. The laboratory did not cook or otherwise heat the refrigerated meat products used for the study before adding them to the simulated stomachs. Dr. Najafi maintains that cooking the meat products was not necessary because each meat came "fully cooked," meaning that it was cooked before being packaged. DE 5698-12 at 13 ("Meats were purchased fully cooked and safe to be consumed as is and hence used in our study as is."). However, Dr. Najafi fails to address the fact that, despite being "fully cooked," the instructions for consuming each meat product directs consumers to, at minimum, heat the product in some way before its consumption. The Court shows below as examples the heating instructions for two of the four meat products that Emery Pharma used for its study:

Considering food preparation methods is particularly important to quantify NDMA exposure, as it has been shown that food preparation can impact NDMA levels in food. *See, e.g.*, Ling Li et al., *Influence of Various Cooking Methods on the Concentrations of Volatile N-nitrosamines and Biogenic Amines in Dry-Cured Sausages*, 77 J. Food Sci. C560, C560 (2012).

In addition, Emery Pharma added only a single meat product to its simulated stomachs, devoid of any condiments or other foods that one would typically think of as comprising a meal. *See* Najafi Dep. at 284 (responding "No" when asked, "Did you test—when you did the hot dog tests, did you consider also testing it with the bun, the condiments and a typical meal eaten with hot dogs to simulate a real-life scenario?"). And finally, the laboratory crushed ranitidine tablets into a powder form before adding them to the simulated stomachs, although Dr. Najafi has pointed to no ranitidine product with instructions for consumers to crush tablets to consume them. The Court shows an example of the consumption directions for one type of Zantac product, which called for a 150 mg tablet to be swallowed whole:

Dr. Najafi does not have any information showing that consumers ignored the heating instructions for refrigerated meat, consumed only a single meat product, and, in conjunction with that unheated meat product, consumed crushed ranitidine. Nor has he explained how such simulated stomach contents have any connection to the stomach contents of ranitidine consumers so as to fit the facts of this case.

The Plaintiffs argue that "there is not one set of 'actual human physiological conditions,'" and that numerous variables, such as diet, stomach capacity, pH level, and health conditions could impact NDMA formation from ranitidine. DE 5914 at 41-42. However, it is the Plaintiffs' burden to explain how the results of Emery Pharma's *in vitro* study can be extrapolated to show that ranitidine forms NDMA in the human stomach. For all of the reasons discussed above, they have not carried that burden.

Although Dr. Najafi reports the results of Emery Pharma's testing with those four meat products, the laboratory also tested ranitidine in combination with other, lower nitrite foods. The full extent of the laboratory's experimentation with other foods is not clear from Dr. Najafi's expert report or the record. What is apparent from the record is that, at minimum, the laboratory also conducted testing with arugula, smoked salmon, and coffee. *See* Najafi Dep. at 282 ("I believe during our development we looked at some, you know, foods. We looked at arugula."); Najafi Dep. Ex. 9 at 31, 42. Beyond a passing reference, Dr. Najafi entirely omits the results of the testing

with these other foods from his expert report. *See* Najafi Report at 104 ("[W]e considered several 'high-nitrate' food products, e.g., Arugula, but they did not influence NDMA formation from ranitidine.").

Dr. Najafi addressed Emery Pharma's testing with foods other than ham, bacon, hotdog, and sausage during his deposition. His explanation of why he did not describe this other testing in his expert report is telling. His testimony reveals that the testing with foods other than ham, bacon, hotdog, and sausage did not produce the outcomes (that is, the levels of NDMA) that he was seeking to include in his report. *See* Najafi Dep. at 283 (testifying that "we just decided that those [other foods] were not—they were not generating, they were not having sufficient nitrite to actually give us the, you know, proper sort of outcomes"); *id.* ("We were looking to see what food . . . would generate NDMA when it comes in contact."); *id.* ("But in my report I'm relying on primarily cooked bacon, sausage, ham. Those types of food.").

Courts have held that such cherry-picking of data demonstrates unreliability and may justify the exclusion of an expert's testimony. *E.g., In re Lipitor (Atorvastatin Calcium) Mktg., Sales Pracs. & Prods. Liab. Litig.*, 892 F.3d 624, 634 (4th Cir. 2018) ("Result-driven analysis, or cherry-picking, undermines principles of the scientific method and is a quintessential example of applying methodologies (valid or otherwise) in an unreliable fashion. Courts have consistently excluded expert testimony that cherry-picks relevant data because such an approach does not reflect scientific knowledge, is not derived by the scientific method, and is not good science." (internal quotation marks and citation omitted)); *EEOC v. Freeman*, 778 F.3d 463, 469-70 (4th Cir. 2005) (Agee, J., concurring) (explaining that "cherry-picking data produces a misleadingly favorable result by looking only to 'good' outcomes" and citing multiple cases to demonstrate that "courts have consistently excluded expert testimony that 'cherry-picks' relevant data").

h. **Miscellaneous Testing**

The majority of the parties' briefing concerns the baseline testing, simulated consumer experience testing, and SGF testing that has been discussed above. However, Emery Pharma also conducted additional studies. For example, Dr. Najafi reports about a "long term refrigeration stability study" where a single ranitidine product was placed in a refrigerator for nine months, and tablets were periodically tested for the presence of NDMA. Najafi Report at 61-62. Dr. Najafi concludes that this refrigeration study "demonstrated no appreciable NDMA formation while the samples were stored in the refrigerator." *Id.* at 62.

The Defendants only briefly address each of these miscellaneous studies in their briefing. *See* DE 5698 at 51-53. The Defendants argue that these studies suffer from the same fatal flaws that the Court has already discussed above, have no connection to the facts at issue in this litigation, and cannot form the basis of any expert's opinions. *Id.* The Plaintiffs respond that the Defendants have inadequately briefed their criticisms of all of these miscellaneous studies. DE 5914 at 51. In any event, all of the Defendants' criticisms are meritless or otherwise go to the weight of the study results rather than to their admissibility. *Id.* at 51-53.

The Court agrees with the Defendants that Emery Pharma's miscellaneous tests suffer from the same fatal flaws as its other tests. Dr. Najafi's expert opinion, to the extent it is based upon the miscellaneous tests, is excluded for all of the reasons set forth above in this section.

In conclusion, the Court has weighed all of the *Daubert* factors. After careful consideration of the totality of the evidence, the Court concludes that Dr. Najafi's expert report is a product of an unreliable methodology and is based upon facts that are not a fit for this case. As a result, Dr. Najafi's expert report is inadmissible under *Daubert* and the Defendants' Najafi Motion is granted as to Dr. Najafi.

2. Experts Relying on Dr. Najafi and Emery Pharma's Testing

a. **Dr. Davis**

Dr. Davis has a Ph.D. in biostatistics, an M.S. in statistics, and a B.A. in mathematics. *See generally* DE 5698-4 at 50-76 (Dr. Davis' curriculum vitae). The Plaintiffs retained Dr. Davis to conduct a statistical analysis of the data from Emery Pharma's baseline testing and simulated consumer experience testing. Davis Report at 2. Dr. Davis' statistical analysis shows, for example, that the mean level of NDMA in the unexpired ranitidine products that Emery Pharma tested during the baseline testing was 1,096.6 ng per 150 mg dose of ranitidine, whereas the median level of NDMA in the same products was 602.7 ng per 150 mg dose of ranitidine. DE 5698-4 at 21. Dr. Davis provided a report dated January 24, 2022, and a rebuttal report dated March 21, 2022. *See* Davis Report; DE 5698-4; Davis Rebuttal Report; DE 5698-5. He was deposed on April 25, 2022. *See* Davis Dep.; DE 5698-17.

The Defendants argue that Dr. Davis' analysis is unreliable and unhelpful because it is based on the data from Emery Pharma's unreliable and unhelpful studies. DE 5698 at 7, 11, 17. And Dr. Davis himself did nothing to verify the validity of Emery Pharma's studies or results. *Id.* at 11, 21, 27-28. The Plaintiffs respond that Dr. Davis' statistical analysis is admissible because it is based on the admissible results of Emery Pharma's ranitidine testing. DE 5914 at 49-50.

Dr. Davis conducted statistical analysis using the data provided to him—the data derived from Emery Pharma's baseline testing and simulated consumer experience testing. Davis Dep. at 51. Dr. Davis did not conduct any testing of ranitidine or ranitidine API himself. *See id.* at 58-59 (testifying that he was not responsible for the collection and generation of the data or for the protocols for that collection and generation). The Plaintiffs do not argue that, if Dr. Najafi's expert opinions are stricken, Dr. Davis' statistical analysis can be salvaged. The Plaintiffs have forfeited

any such argument. *See Hollis*, 2022 WL 4124300, at *7 ("It is well settled that a party who fails to respond to an argument in her response necessarily forfeits the point.").

Given the Court's conclusion that Dr. Najafi's expert opinion based on Emery Pharma's unreliable and unhelpful testing methodologies is inadmissible, Dr. Davis' statistical analysis is likewise inadmissible. The Defendants' motion seeking to strike Dr. Davis' general causation opinion is therefore granted.

b. **Drs. Le, Salmon, Panigrahy, McTiernan, and Moorman**

The Defendants identify three of the Plaintiffs' experts who, according to the Defendants, rely on data from Emery Pharma's testing as part of their general causation opinions: Drs. Le, Salmon, and Panigrahy. DE 5698 at 17 n.19. Dr. Le discusses Emery Pharma's baseline testing and simulated consumer experience testing in her expert report. *See* Le Report at 56-60. She explains that that the levels of NDMA that Emery Pharma measured during its studies strengthen her opinions that the ingestion of ranitidine exposes consumers to substantial levels of NDMA and that ranitidine is capable of causing cancer. *Id.* at 10.

Dr. Salmon also discusses Emery Pharma's baseline testing and simulated consumer experience testing in his expert report. Salmon Report at 215-20. He concludes:

> Based on the levels of NDMA reported by Emery Pharma and FDA to occur in ranitidine medications both as supplied and after storage under conditions simulating consumer handling, it appears that users of ranitidine were exposed to levels as great or greater than the levels observed to cause bladder, esophageal, liver, pancreatic and stomach cancer in people exposed to NDMA.

Id. at 5. *But see* Salmon Rebuttal Report at 1; DE 5692-3 at 1180 (explaining that he "undertook a causation analysis based on the totality of the evidence" and that Emery Pharma's "testing results further support [his] opinions but are not the basis for them.").

Dr. Panigrahy uses the mean level of NDMA detected during Emery Pharma's baseline testing of unexpired ranitidine products to calculate what lifetime cumulative NDMA exposure could be if a person taking ranitidine were to ingest 1,096.6 ng of NDMA per 150 mg dose of ranitidine. Panigrahy Report at 198-99. He concludes that "[t]hese lifetime cumulative exposures to NDMA are the basis for [his] opinions that when reached or exceeded by humans there is a statistically significant increased risk" of bladder, esophageal, gastric, liver, and pancreatic cancer. *Id.* at 199.

In addition to pointing to Drs. Le, Salmon, and Panigrahy, the Defendants identify two additional experts for the Plaintiffs—Drs. McTiernan and Moorman—who, according to the Defendants, state that the data from Emery Pharma's studies supports their general causation opinions. DE 5698 at 17 n.19. Dr. McTiernan explains in her expert report that, while her causation opinions are not predicated on the levels of NDMA detected during Emery Pharma's testing, the laboratory's test results strengthen her causation opinions. McTiernan Report at 14. Dr. Moorman states in her expert report that her "causation opinions in this case are based on NDMA levels as tested by FDA and by the ranitidine manufacturers" "[t]o be conservative," but that, "[i]f the amount of NDMA that is formed in the tablets is in the range being reported by Emery, it would further strengthen [her] opinion based on dose-response considerations." Moorman Report at 37; DE 5692-1 at 568.

The Defendants contend that the expert opinions of Drs. Le, Salmon, Panigrahy, McTiernan, and Moorman must be stricken to the extent that those opinions rely on the results of Emery Pharma's ranitidine testing and on Drs. Najafi and Davis' expert opinions. DE 5698 at 7. The Plaintiffs make no argument to the contrary and therefore have forfeited any such argument. *See Hollis*, 2022 WL 4124300, at *7.

In light of the Plaintiffs' failure to respond, the expert opinions are stricken to the extent that those opinions rely on the results of Emery Pharma's ranitidine testing. The Court explains the ramifications of its ruling on Emery Pharma's testing as to the opinions of Drs. Moorman and McTiernan in Section VI(A)(3)(b)(iii), *infra*.

3. Final Ruling on Plaintiffs' Internal Testing

For all of the reasons set forth in this Order, including the Court's rulings on secondary evidence and primary evidence, *see infra* Sections VI-VII, the Brand Defendants' Motion to Exclude the Opinions and Testimony of Plaintiffs' Experts, Ramin Najafi, PH.D., Charles Davis, PH.D., and Other Experts who Rely on Their Opinions [DE 5698; DE 5732] is granted. In addition to proffering Dr. Najafi's opinions to prove how much NDMA people are exposed to from taking ranitidine, the Plaintiffs seek to admit expert testimony that relies upon scientific studies,[54] other than those performed by Dr. Najafi, to prove that NDMA forms endogenously from ranitidine.[55] In other words, the Plaintiffs' experts rely upon these studies to argue that ranitidine transforms into NDMA made from chemical processes within the stomach after ingestion. The Court now turns to those opinions.

B. External Testing for Endogenous Formation of NDMA

Five of the Plaintiffs' experts opine that NDMA can form inside the digestive tract after ingestion of ranitidine: Drs. Panigrahy, Michaels, Marletta, Le, and Najafi. Panigrahy Report at 83-118; Michaels Report at 2, 32, 58-61; Marletta Report at 40-41; Le Report at 70; Najafi Report at 93. These experts opine that ranitidine transforms into NDMA inside the digestive tract through

[54] Throughout this Order, the Court refers to scientific studies by the last name of the first listed author.

[55] These studies are mechanistic evidence, a form of secondary evidence. The Plaintiffs rely on much secondary evidence to support their claims about (1) the amount of NDMA at issue in this MDL and (2) that ranitidine causes cancer. In this subsection, the Court assesses the Plaintiffs' secondary evidence about the amount of NDMA at issue. The Court assesses the rest of the Plaintiffs' secondary evidence in Section VII, *infra*.

a chemical process called "nitrosation." Nitrosation is a chemical reaction in which organic compounds are converted into nitroso compounds. Nitroso compounds are chemical compounds containing a nitroso group (-N=O). There are different types of nitroso compounds. One group of nitroso compounds is known as "nitrosamines." Nitrosamines are formed by the reaction of certain compounds, called secondary and tertiary amines, with a nitrosating agent. NDMA is one type of nitrosamine that can be formed from this process. According to the Plaintiffs' experts, ranitidine contains a tertiary amine, enabling it to undergo nitrosation to form NDMA.

The Plaintiffs' experts opine that there are two possible ways that ranitidine can undergo nitrosation to form NDMA in the digestive tract. First, they explain that nitrosation can occur when ranitidine is combined with nitrites in stomach acid to create conditions that initiate the nitrosation process. *See, e.g.*, Panigrahy Report at 84-85. Second, the Plaintiffs' experts propose that nitrosation of ranitidine can occur when ranitidine comes into contact with bacteria in the stomach. They explain that acid-reducing medications, such as H2-blockers and PPIs, block the production of stomach acid, which increases the stomach's pH and leads to an overgrowth of bacteria in the gut, promoting nitrosation of ranitidine. *See, e.g.*, *id.* According to the Plaintiffs' experts, both mechanisms of nitrosation depend on individualized factors such as diet, stomach pH, the presence of certain chemicals in saliva, and the levels of nitrite and bacteria in the gut. *Id.*

In support of their theory of endogenous formation of NDMA from ranitidine, the Plaintiffs' experts rely upon two types of studies: *in vivo*—studies conducted on live human subjects, and *in vitro*—studies conducted using simulated conditions in a lab. *See, e.g.*, *Reference Manual on Scientific Evidence*, *supra*, at 682. The Defendants object to the Plaintiffs' experts' reliance on both *in vivo* and *in vitro* evidence and seek to exclude the Plaintiffs' experts' opinions that ranitidine can transform into NDMA endogenously. The Court addresses the Plaintiffs' *in*

vivo and *in vitro* studies separately as follows: the Court provides a general summary of each study, the arguments that the parties make regarding the Plaintiffs experts' reliance on the studies, and then the Court's analysis and determination of whether the Plaintiffs' experts may rely upon the study to opine that NDMA can form endogenously from ranitidine.

1. *In Vivo* Studies

All five of the Plaintiffs' experts who opine that NDMA forms endogenously from ranitidine rely upon *in vivo* studies in support of their opinions. In these studies, human subjects were administered ranitidine, other H2-blockers, and/or NDMA and then were evaluated to determine how much NDMA was in their bodies. Depending on the particular study, researchers took measurements of the NDMA in participants' urine, plasma, and/or gastric juice. The Defendants argue that the *in vivo* studies that the Plaintiffs' experts rely upon do not constitute a reliable scientific basis for their endogenous formation opinions. These studies are described below.

a. ***In Vivo* Studies Identified by the Parties**

The Defendants address six specific *in vivo* studies in making their argument that the Plaintiffs' experts should be precluded from opining that ranitidine can transform into NDMA endogenously: Zeng & Mitch,[56] Spiegelhalder,[57] Matsuda,[58] Krawczynski,[59] Florian,[60] and Mitch & Najafi.[61] *See generally* DE 5696; DE 5913; DE 5960. Although these are the only *in vivo* studies that the Defendants addressed, the Plaintiffs assert in their Response that their experts also relied

[56] Teng Zeng & William A. Mitch, *Oral Intake of Ranitidine Increases Urinary Excretion of N-nitrosodimethylamine*, 37 Carcinogenesis 625 (2016).
[57] B. Spiegelhalder et al., *Urinary Excretion of N-nitrosamines in Rats and Humans*, 41 IARC 443 (1982).
[58] Jun Matsuda et al., *N-nitrosamines in Gastric Juice of Patients with Gastric Ulcer Before and During Treatment with Histamine H2-receptor Antagonists*, 25 Gastroenterologia Japonica 162 (1990).
[59] Marian Krawczynski et al., *Nitrosamines in Children with Chronic Gastritis*, J. Polish Paediatric Soc'y 1 (2002).
[60] Florian et al., *supra*.
[61] Brown Decl., DE 5692, Supplement 6, Ex. 112, Ex. 113.

upon additional *in vivo* studies to inform their endogenous formation opinions.[62] DE 5913 at 6 nn.9-10. The Plaintiffs listed those additional studies but did not describe them or make any arguments that they constitute reliable *in vivo* evidence of endogenous formation. As such, the Court will not describe those studies here but will nonetheless address the Plaintiffs' experts' reliance on them below. The Court proceeds to describe only the six studies specifically addressed by the Plaintiffs' and Defendants' arguments in their briefing.

i. Zeng & Mitch

The first *in vivo* study that the Plaintiffs' experts rely upon in support of their endogenous formation theory is Zeng & Mitch. Zeng & Mitch measured how much NDMA was excreted in the urine of volunteers administered clinical ranitidine doses. Teng Zeng & William A. Mitch, *Oral Intake of Ranitidine Increases Urinary Excretion of N-nitrosodimethylamine*, 37 Carcinogenesis 625, 625 (2016).[63] Researchers collected urine samples from ten healthy adult volunteers over 24-hour periods before and after ingestion of 150 mg of ranitidine. *Id.* They then analyzed the urine samples for NDMA using gas chromatography-mass spectrometry ("GC-MS"). *See Retraction*, 42 Carcinogenesis 1008 (2021) [hereinafter *Retraction*]. The study authors reported that urinary excretion of NDMA increased 400-fold after ingestion of ranitidine. *Id.* at 625, 627, 633. They concluded that because only about 0.05% of NDMA is excreted in urine, "[a]ctual systemic NDMA exposure is likely much higher than that eliminated in urine" and

[62] In their Response, the Plaintiffs cite to the following studies: Steve E. Hrudey et al., *Drinking Water as a Proportion of Total Human Exposure to Volatile N-nitrosamines*, 33 Risk Analysis 2179 (2013); F. Garcia Del Risco et al., *The Effect of Ranitidine Over a 24-Hour Period on the Content of Nitrites, Nitrates, Nitrosamines and on the Bacterial Flora of The Gastric Juice in Healthy Subjects*, 8 Gastroenterologie Clinique et Biologique 749 (1984); Houben et al., *Are Intragastric N-nitroso Compounds Elevated After Short-Term Acid Suppression*, 5 Eur. J Cancer Prevention 83 (1996); J. Meyrick Thomas et al., *Effect of One Year's Treatment with Ranitidine and of Truncal Vagotomy on Gastric Contents*, 28 Gut 726 (1987); D. L. Morris et al., *Mutagenicity in Gastric Juice*, 7 Gut 723 (1984); H. J. O'Connor et al., *Effect of Histamine H2-receptor Antagonist Therapy on the Mutagenic Activity of Gastric Juice*, Mutation Rsch., 188 (1987). DE 5913 at 6 nn.9-10.

[63] The Court referred to this study as a Stanford University study in its Introduction, Section I.

cautioned that "a more comprehensive risk assessment" of ranitidine was necessary given its widespread use and the potential cancer risk. *Id.* at 631-33.

In 2021, Drs. Zeng and Mitch issued a formal retraction of this study because the use of gas chromatography to measure NDMA formation could have itself contributed to the levels of NDMA that were measured. *Retraction*, *supra*, at 1008. Therefore, the NDMA measurements from the 2016 study could not be considered reliable. *Id.* The FDA reached the same conclusion, stating that GC-MS is not a "suitable" method for testing ranitidine because it generates artefactual NDMA.[64]

ii. Spiegelhalder

The Plaintiffs' experts' second *in vivo* study in support of their endogenous formation theory is Spiegelhalder. In Spiegelhalder, researchers measured the amount of NDMA excreted in the urine of three volunteers before and after administration of NDMA-containing beverages. B. Spiegelhalder et al., *Urinary Excretion of N-nitrosamines in Rats and Humans*, 41 IARC 443, 443-44 (1982). The volunteers were administered various doses of NDMA in beer, orange juice, and orange juice with 6% ethanol. *Id.* at 446. The study authors reported that between 0.5 and 2.4% of the dose of NDMA administered was excreted in the urine of the volunteers who were administered NDMA with alcohol. *Id.* There was no NDMA detected in the urine of volunteers administered NDMA with orange juice. *Id.* The authors noted that they had a 0.05 µg/l detection limit for NDMA,[65] and so the excretion values for NDMA could be estimated as being less than 0.05% of the administered dose. *Id.* The authors state that "[t]o detect NDMA exposure by urine

[64] FDA, *Updates and Press Announcements on NDMA in Zantac (Ranitidine)*, https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine (last visited June 12, 2022); Press Release, FDA, Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) Method for the Determination of NDMA in Ranitidine Drug Substance and Drug Product (Sept. 13, 2019) ("As GC based methods had been observed to elevate NDMA levels in tested materials an alternative method which prevents the degradation of ranitidine and the subsequent formation of NDMA was therefore needed.").

[65] 0.05 µg/l is equivalent to 50 ng/l.

monitoring, single doses would have to be of the order of hundreds of micrograms, unless excretion rates are increased by the administration of ethanol." *Id.*

iii. Matsuda

The third *in vivo* study relied upon by the Plaintiffs' experts is Matsuda. Matsuda is a peer-reviewed study that tested nitrosamine levels, including levels of NDMA, in the gastric fluid of 72 healthy human subjects and 279 human subjects with gastric ulcers at various stages of ulceration. Jun Matsuda et al., *N-nitrosamines in Gastric Juice of Patients with Gastric Ulcer Before and During Treatment with Histamine H2-receptor Antagonists*, 25 Gastroenterologia Japonica 162, 162 (1990). At the first analysis of the subjects' gastric juice, 121 subjects were in the active phase, 98 in the healing phase, and 60 in the scarring phase. *Id.* at 163. At endoscopy, most patients were given conventional treatment with anticholinergics and antacids. *Id.* On diagnosis of gastric ulcers, subjects were prescribed a regular dosage of H2-blockers in addition to continuing their conventional treatment. *Id.* When subjects' ulcers healed to the scarring stage, the dosage of H2-blockers was halved and maintained thereafter. *Id.*

Researchers took varying numbers of samples of subjects' gastric juice at different durations of H2-blocker administration (0-2 months, 2-6 months, 6-12 months, and 12-36 months). *Id.* at 165. Subjects underwent an overnight fast of at least 12 hours before endoscopy. *Id.* at 163. Then the researchers analyzed the subjects' gastric juice immediately after collection. *Id.* The nitrosamine levels were measured by chemiluminescent method using a thermal energy analyzer combined with gas chromatography. *Id.* Temperatures used during the gas chromatography ranged between 175°C and 200°C. *Id.*

Researchers reported a statistically significant increase in the detection ratios of intragastric NDMA in patients on H2-blockers at the healing stage in comparison with patients not taking H2-

blockers. *Id.* at 165. The study authors stated that the reason for the increase in nitrosamine levels at the healing stage was not clear, and that "additional unknown factor(s) may be important for determination of [nitrosamine] levels in the stomach." *Id.* at 167. Additionally, researchers reported finding similar levels of NDMA regardless of the H2-blocker administered. *Id.* at 166-67. They stated that "[e]ach H2-blocker showed similar intragastric NA levels, which indicated that the effects on gastric nitrosation were the same by regular dosages of these drugs." *Id.* at 167. In other words, the authors concluded that all four H-2 blockers—ranitidine, cimetidine, famotidine, and roxatidine—formed NDMA at similar rates, and "[t]here was no particular difference among any of these H2-blockers." *Id.* at 166. They concluded that ranitidine did not uniquely degrade into NDMA in the digestive tract. *Id.*

iv. Krawczynski

The final *in vivo* study relied upon by the Plaintiffs' experts, and highlighted by the Defendants, is Krawczynski. Krawczynski is a published *in vivo* study designed to evaluate the concentration of nitrosamines in the gastric juice in children in Poland with chronic gastritis before and after treatment with H2-blockers. Marian Krawczynski et al., *Nitrosamines in Children with Chronic Gastritis*, J. Polish Paediatric Soc'y 1, 1 (2002). The study was conducted in two groups of 30 children each. *Id.* at 3. The children in the first group had chronic gastritis and H. pylori infection. *Id.* The children in the second group had abdominal pain without changes in gastroscopic examination. *Id.* Researchers treated the children in the first group with ranitidine for 28 days, as with amoxicillin and nitroimidazole for 7 of those days, then 4-6 weeks after the conclusion of treatment, tested the children's gastric juices for various nitrosamines, including NDMA. *Id.* Researchers used GC-MS to measure the amounts of nitrosamines in the children's gastric juice and urine. *Id.*

The study authors reported a statistically significant increase in nitrosamine concentration in the gastric juice of the children with gastritis after treatment with ranitidine, amoxicillin, and nitroimidazole compared to pre-treatment values as well as compared to the control group. *Id.* at 4. They also reported a statistically significant urinary excretion of nitrosamines in boys only after treatment in comparison to pre-treatment values as well as compared to the control group. *Id.* The authors did not calculate the concentrations of individual nitrosamines. The authors concluded that, "[i]n view of the potential negative effect of nitrosamines on the condition of gastric mucosa, the anti-Hp triple therapy, including the use of H2-blockers, can be recommended in children only after careful consideration." *Id.* at 8.

v. Florian

In contrast to the *in vivo* studies relied upon by the Plaintiffs' experts and detailed above, the Plaintiffs' experts assert that they do not rely upon Florian. Florian is a published, peer-reviewed, and placebo-controlled clinical study that was conducted to evaluate the amount of NDMA excreted in the urine of 17 participants after ingesting ranitidine compared with placebo. Florian et al., *supra*, at 240. The participants were randomized into one of four treatment groups: (1) placebo with non-cured meats diet, (2) placebo with cured meats diet, (3) 300 mg ranitidine with non-cured meats diet, and (4) 300 mg ranitidine with cured meats diet. *Id.*

Participants underwent four rounds of treatment throughout the course of the study. *Id.* at 241. For each round, participants consumed their assigned diet on pretreatment days, underwent an overnight fast, then took either ranitidine or a placebo and began eating breakfast one minute later. *Id.* According to the study authors, because the formation of NDMA is dependent upon the presence of nitrite and acidic conditions, this methodology was intended to maximize the amount of nitrite and acid in the volunteers' stomachs. *Id.* After treatment administration, researchers

collected all urine excreted by the volunteers over a period of 24 hours. *Id.* at 242. They also collected thirteen blood samples from each volunteer at set times on each treatment day. *Id.* The researchers then measured the concentrations of NDMA, DMA, and ranitidine in the urine and blood plasma using liquid chromatographic tandem mass spectrometric methods ("LC-MS"). *Id.*

For volunteers given the cured meats diet, the researchers measured a median of 11.9 ng NDMA in the urine of those who took ranitidine and 23.4 ng NDMA for those who took placebo. *Id.* at 244. For the volunteers given the non-cured meats diet, researchers measured a median of 0.6 ng NDMA in the urine of the ranitidine group, and 10.5 ng NDMA in the urine of the placebo group. *Id.* The authors of the study conducted a statistical analysis and concluded that "[t]here was no statistically significant difference between the ranitidine and placebo in 24-hour urinary excretion of NDMA with a noncured-meats diet . . . or a cured meats diet." *Id.* In other words, "oral administration of ranitidine (300 mg) did not significantly increase 24-hour urinary excretion of NDMA." *Id.* at 246. On the other hand, the authors did find that there was a statistically significant difference in the amount of NDMA observed between the volunteers consuming cured meat diets as opposed to non-cured meats diets. *Id.* The authors concluded that their finding of a significant increase in NDMA urinary excretion on a cured-meats diet "suggest[ed] that the study design and methods were sufficiently sensitive to detect the relatively small effect of diet on NDMA urinary excretion." *Id.* at 247.

vi. Mitch & Najafi

The second *in vivo* study cited by the Defendants, but not relied upon by the Plaintiffs' experts, is Mitch & Najafi. This study was conducted by Dr. Mitch, one of the authors of Zeng & Mitch, and Dr. Najafi, one of Plaintiffs' experts.[66] Brown Decl., DE 5692 Supplement 6 Ex. 112

[66] There were five additional authors of this study.

at 1313. Mitch & Najafi was neither published nor peer reviewed. According to the Plaintiffs, the study was shut down before it could be completed because the Stanford Institutional Review Board approval was revoked in light of the FDA's recall of ranitidine. DE 5913 at 7 n.12.

In the unpublished draft manuscript, the authors explain that they administered Zantac to eight volunteers and collected urine samples over a period of 24 hours following Zantac ingestion. Brown Decl., DE 5692 Supplement 6 Ex. 112 at 1330. They determined that "[a]ll 8 volunteers did not demonstrate any detectable levels of NDMA following consumption of ranitidine throughout the 24-hour collection period." *Id.* at 1330-31. The study authors also stated that "[t]he absence of NDMA in urinary excretions however, does not rule out in vivo formation of NDMA from ranitidine." *Id.* at 1331.

b. **Plaintiffs' Experts' Reliance on the *In Vivo* Studies**

The Defendants make two arguments in support of their claims that the *in vivo* studies that the Plaintiffs' experts rely upon do not constitute a reliable scientific basis for their endogenous formation opinions. First, the Defendants argue that the Plaintiffs' experts employed unreliable scientific methodologies to review and weigh the *in vivo* studies that they rely upon in support of their endogenous formation opinions. *See* DE 5696 at 12; DE 5960 at 8-10. Specifically, the Defendants argue that the Plaintiffs' experts' reasons for disregarding Florian are "internally inconsistent and based on studies that do not support the experts' conclusions." *See* DE 5696 at 10-12; *see also* DE 5960 at 6. Second, the Defendants argue that the *in vivo* studies that the Plaintiffs' experts rely upon are unreliable evidence of endogenous formation. *See* DE 5696 at 10; *see also* DE 5960 at 6. These two arguments and the Plaintiffs' responses to these arguments are evaluated below.

i. Plaintiffs' Experts' Methodologies for Weighing *In Vivo* Studies

A. Parties' Arguments

The Defendants argue that the Plaintiffs' experts employed unreliable methodologies when weighing the *in vivo* studies that they rely upon to opine that NDMA can form endogenously from ranitidine. They further contend that the Plaintiffs' experts' reasons for discounting Florian are inconsistent and the studies that the experts rely upon used "outdated and insensitive methods." DE 5960 at 11; DE 5696 at 11. Additionally, the Defendants note that when Drs. Marletta and Melnick were asked what evidence they found more reliable than Florian for determining endogenous formation of NDMA from ranitidine, Dr. Marletta pointed only to *in vitro* studies, and Dr. Melnick conceded that Florian is the best available evidence on endogenous NDMA formation. DE 5696 at 11.

The Plaintiffs respond by emphasizing that their experts reliably applied weight-of-the-evidence methodologies and by arguing that the Defendants commit "two fundamental errors." *See* DE 5913 at 16, 19, 21. The first error, the Plaintiffs contend, is that the Defendants impermissibly "ask[] the Court to judge Plaintiffs' experts based on only one type of evidence: the urine studies." *Id.* According to the Plaintiffs, the Court may only assess whether the Plaintiffs' experts "faithfully followed" their weight of the evidence methodologies. *Id.* at 17, 22. The second error is that the Defendants impermissibly ask the Court to assign higher weight to *in vivo* studies measuring NDMA in urine than to other *in vivo* studies. *Id.* at 21.

B. Analysis

i. Court's Role in Evaluating Weight-of-the-Evidence Methodology

As a threshold matter, the Court addresses the Plaintiffs' assertion that the Court is not permitted to examine their experts' individual studies and that the Court's role is limited to

examining whether the Plaintiffs' experts considered a variety of evidence, weighed it carefully, and provided scientific explanations for their decisions. The Plaintiffs are incorrect.

As part of the Court's gatekeeping role to ensure that speculative and unreliable opinions do not reach the jury, *see supra* Section III(A), the Court must evaluate the process of *how* an expert *applied* her methodology. *Magistrini*, 180 F. Supp. 2d at 602 ("While flexible application of the *Daubert* factors permits this Court to find that, properly applied, the weight-of-the-evidence methodology is not an unreliable methodology, in order for [the expert]'s opinion to go to a jury, the *application* of that methodology also must be reliable."). This does not mean the Court's role is limited to determining whether the expert relied upon a "wide array" of evidence, especially since the quantity and variety of evidence proffered by an expert does not establish the reliability of the expert's evidence. *See In re Abilify* (*Aripiprazole*) *Prods. Liab. Litig.*, 299 F. Supp. 3d 1291, 1311-12 (N.D. Fla. 2018) ("[A]n expert cannot merely aggregate various categories of otherwise unreliable evidence to form a reliable theory of general causation."). Rather, "every aspect of the expert's analysis—including his methodology, the combination of facts and scientific evidence on which he relies, and the links between the evidence and his conclusions—must be shown to satisfy Rule 702 and *Daubert*." *Id.* at 1312.

As such, the Court may consider the reliability of the individual studies themselves, as well as the Plaintiffs' experts' processes for evaluating and weighing the studies, to determine whether the studies reliably support the conclusions reached by the Plaintiffs' experts. *See id.* at 1311-12; *see also Siharath*, 131 F. Supp. 2d at 1368-69. This does not mean that the Court would be, as the Plaintiffs argue, "judg[ing] causation based exclusively on the urine studies." *See* DE 5913 at 22. Nor does it mean the Court would be deciding what weight should be afforded to a particular study. Instead, the Court's role is to consider *all* of the evidence relied upon by the Plaintiffs' experts,

including the *in vivo* evidence, and to determine whether the evidence reliably and helpfully informs the expert's general causation question.

For an expert's application of the weight of the evidence methodology to be reliable, the expert must:

> (1) identify an association between an exposure and a disease, (2) consider a range of plausible explanations for the association, (3) rank the rival explanations according to their plausibility, (4) seek additional evidence to separate the more plausible from the less plausible explanations, (5) consider all of the relevant available evidence, and (6) integrate the evidence using professional judgment to come to a conclusion about the best explanation.

Abilify, 299 F. Supp. 3d at 1311 (quoting *Milward v. Acuity Specialty Prods. Grp., Inc.*, 639 F.3d 11, 18 (1st Cir. 2011)). Due to the "substantial judgment" required of an expert in following this approach, "it is crucial that the expert describe each step in the process by which he gathered and assessed the relevant scientific evidence." *Id.* at 1311.

The Plaintiffs' experts have not "describe[d] each step in the process by which [they] gathered and assessed the relevant scientific evidence," including their process for assessing the *in vivo* studies of endogenous formation. *See id.* The Plaintiffs merely assert that their experts applied their "careful judgment" and gave "scientifically grounded reasons" in assigning weight to each study. DE 5913 at 4-5. In fact, the Plaintiffs refer the Court generally to the experts' reports, insinuating that the reports contain voluminous pages explaining the rationales underlying each experts' weighing of each study. *See* DE 5913 at 17, 19 ("It would be tedious (and likely violate the local rule's page count requirements) to catalogue here every rationale for every expert's weighting of every study.").

After a careful review of the expert reports, the Court has been unable to find any significant descriptions of the steps that the Plaintiffs' experts took when gathering and assessing studies. Each of the experts provide only bare-bones description of their methodologies. For

example, Dr. Le explains in her report that she formulated her conclusions by "reviewing available scientific literature and data" and then "using weight-of-the-evidence methodology to analyze the information." Le Report at 7. She stated:

> My opinions are based on my comprehensive review of published studies, internal reports and materials provided to me regarding this case. Applying evidence-based medicine that focuses on scientific and objective data, I critically evaluated studies and materials related to the pharmacokinetics-pharmacodynamics, toxicology, and epidemiology of ranitidine and NDMA as they pertain to cancer development to deliberate on general causation. Balancing the quality, number and diversity of studies and information, I opine that the chronic use of ranitidine contributes to the development of certain cancers. My reasons for deriving to this conclusion are provided below and based on evidentiary materials.

Id. at 8. Following this paragraph, Dr. Le gives her substantive analyses and conclusions based on the scientific data. *See id.* Dr. Le's description of her methodology does not inform the Court of each step she took in her gathering and weighing process. None of the Plaintiffs' endogenous formation experts provide descriptions sufficient to inform the Court of the steps he or she took in gathering and assessing the relevant studies.[67] Without such descriptions, the Court is unable to determine whether the Plaintiffs' experts' methodologies were based on scientific procedure, or on "subjective belief or unsupported speculation." *In re Abilify*, 299 F. Supp. 3d at 1311.

The Plaintiffs' experts' failure to detail the steps that they took in gathering and assessing the scientific literature limits the Court's ability to fulfill its gatekeeping role to ensure that the experts' general causation opinions are based on a reliable methodology. This factor weighs strongly against the admissibility of the Plaintiffs' experts' endogenous formation opinions. Nonetheless, the Court continues to analyze the Plaintiffs' experts' opinions and the parties' arguments.

[67] *See* Michaels Report at 3-4; Marletta Report at 4-5; Najafi Report at 6-7; Panigrahy Report at 10-15.

ii. Plaintiffs' Experts' Methodologies for Evaluating **In Vivo** *Evidence*

All five of the Plaintiffs' experts who opined that NDMA can form endogenously from ranitidine "under-weighted," or in other words discounted, Florian's results. DE 5913 at 20. Their reasons for discounting Florian are internally inconsistent with their decisions to rely upon and assign greater weight to other *in vivo* studies.

First, the Plaintiffs' experts are inconsistent in their analyses of the number of participants in the *in vivo* studies. Dr. Najafi discounts Florian in part because the study considered 17 healthy volunteers, which he states, "cannot be said to reflect the United States population with varying different stomach chemistries and diets." Najafi Report at 109. The Plaintiffs themselves echoed this criticism at oral argument, stating: "[O]ur experts opine [Florian] is a small study. It is only 17 healthy participants who don't resemble the Ranitidine population or their gastric environment." Defendants' Sept. 22 *Daubert* Hearing Tr. at 45-46. However, all five endogenous formation experts rely upon Spiegelhalder, which only studied 3 participants. *See supra* Section V(B)(1)(a).[68] Additionally, Drs. Marletta, Michaels, and Panigrahy rely upon Garcia del Risco, which only studied 4 subjects, and Drs. Marletta and Panigrahy rely upon Thomas, which studied only 15 unhealthy subjects and 11 controls. *See* Michaels Report at 31; Marletta Report at 43; Panigrahy Report at 86-87, 95-100; *supra* note 62. Neither the Plaintiffs nor their experts provide any rationale as to why the size of the participant group in Florian was too small, on the one hand, and the size of the participant groups in Spiegelhalder, Garcia del Risco, and Thomas were not problematic, on the other hand. The Plaintiffs neither reconcile nor acknowledge this inconsistency in their experts' methodologies.

[68] *See* Najafi Report at 109; Le Report at 44; Marletta Report at 45-46; Michaels Report at 50-51; Panigrahy Report at 83.

A second inconsistency in the Plaintiffs' experts' methodologies for weighing studies is how they factor in the role Vitamin C may have played in study outcomes. Drs. Najafi, Michaels, Marletta, and Le underweight Florian because the study did not properly control for the amount of Vitamin C and Vitamin E in the subjects' diets, vitamins that they claim inhibit nitrosation and prevent the formation of NDMA. *See* Najafi Report at 109; Michaels Report at 59; Marletta Report at 55-56; Le Report at 43. Despite this assertion, the Plaintiffs' experts rely on Spiegelhalder, a study in which subjects were administered ranitidine with orange juice, beer, and orange juice with ethanol before measuring the amount of NDMA excreted in urine. *See supra* Section V(B)(1)(a)(ii); *see also* DE 5913 at 6; Najafi Report at 109; Michaels Report at 60; Marletta Report at 45-46; Le Report at 36,44. The Plaintiffs' experts rely on this study principally to opine that NDMA cannot be measured in the urine, and, thus, to discount the findings of Florian. However, neither the Plaintiffs nor their experts explain why the Vitamin C in the subjects' diets in Florian is a reason to discount that study, yet the Vitamin C present in subjects' *orange juice* is not a reason to discount Spiegelhalder. Moreover, the Plaintiffs' experts do not address whether, if Vitamin C inhibits NDMA formation, Vitamin C could be the reason in Spiegelhalder why NDMA was not detected in the urine, rather than their conclusion that NDMA cannot be detected in urine.

A third inconsistency in the Plaintiffs' experts' methodologies for weighing the *in vivo* studies of endogenous formation relates to their conclusions regarding the metabolism of NDMA. Four of the Plaintiffs' experts, Drs. Panigrahy, Michaels, Marletta, and Najafi, discount the results of Florian because, according to them, NDMA is rapidly metabolized in the body and thus is inherently difficult to measure in urine and blood plasma. DE 5913 at 20; Najafi Report at 107, 109. The fifth expert, Dr. Le, discounts the results of Florian because a "lack of urinary concentration cannot be interpreted as [a] lack of plasma or blood concentration of NDMA." DE

5913 at 20 (alteration in original) (quoting Le Report at 36, 44). The Plaintiffs explained at oral argument that their experts criticize Florian because the study tested participants' blood plasma for NDMA. Defendants' Sept. 22 *Daubert* Hearing Tr. at 56. The Plaintiffs explained that their experts opine that NDMA forms and metabolizes in the gastrointestinal tract without ever reaching the blood. *Id.* at 56-58 ("Florian is only determining if NDMA has formed by measuring the blood, and what happens to NDMA is that it is rapidly metabolized by the human body and it never reaches the plasma.").

The Plaintiffs' experts' criticisms of the plasma measurements in Florian contradict other opinions that they provide in this litigation. Dr. Le opines that over 90 percent of NDMA passes into the bloodstream after being orally ingested. Le Report at 9. This opinion contradicts the Plaintiffs' statement that NDMA is rapidly metabolized by the human body, and it never reaches the plasma. DE 5913 at 6; Najafi Report at 109. Additionally, the Plaintiffs' experts' criticisms of the plasma measurements in Florian contradict their reliance on animal studies, which were conducted based upon the measurement of NDMA in animal blood. *See infra* Section VII(A).

Moreover, the Plaintiffs themselves rely on the blood plasma data from Florian to argue that, despite the limitations of Florian, its findings support the conclusion that NDMA forms endogenously from ranitidine. DE 5913 at 7-8 ("In Florian, *et al.*, ranitidine and nitrite combined to form NDMA in the ranitidine treatment group, just as Plaintiffs' experts opine."). It is internally inconsistent for the Plaintiffs to pull individual data points from a study in support of their own conclusions, while simultaneously arguing that the same study is unreliable and that it must be discounted as a whole. *In re Lipitor*, 892 F.3d at 634 ("Result-driven analysis, or cherry-picking, undermines principles of the scientific method and is a quintessential example of applying methodologies (valid or otherwise) in an unreliable fashion. Courts have consistently excluded

expert testimony that cherry-picks relevant data because such an approach does not reflect scientific knowledge, is not derived by the scientific method, and is not good science." (internal quotation marks and citation omitted)).

ii. Reliability of *In Vivo* Studies

A. Parties' Arguments

The Defendants' second argument as to why the *in vivo* studies that the Plaintiffs' experts relied upon do not constitute a reliable basis for endogenous formation opinions is that the studies themselves are unreliable. They assert that Zeng & Mitch is unreliable because it measured NDMA using GC-MS testing. DE 5696 at 8. Next, the Defendants argue that Matsuda does not reliably support the Plaintiffs' experts' opinions. *Id.* at 10-11. And, while Dr. Panigrahy relies on this study in his expert report, he ultimately admitted that Matsuda did not support his hypothesis. *Id.*

The Plaintiffs respond that, "[d]ue to the significant limitations of the urine studies, Plaintiffs' experts supplemented these studies with other types of evidence that evaluated endogenous formation of NDMA." DE 5913 at 6. Specifically, the Plaintiffs refer to studies that measured concentrations of nitrosamines, including NDMA, in gastric juice, stating that the studies "consistently demonstrated that NDMA forms endogenously." *Id.* The Plaintiffs list the majority of these studies in a footnote and do not argue why they are reliable.[69] *See id.* at 6-7.

Further, the Plaintiffs asserted in their Response that two of the *in vivo* studies, Krawczynski and Matsuda, demonstrate that NDMA forms endogenously and the Plaintiffs provided short descriptions of the measurements of nitrosamines in each study. *See id.* But, they did not argue that Matsuda and Krawczynski are reliable. The Plaintiffs argued that these studies

[69] *See supra* note 62 and accompanying text.

are reliable for the first time during oral argument. They argued that Matsuda and Krawczynski are reliable because the studies are peer reviewed and because the studies have been accepted in the medical and scientific communities. Defendants' Sept. 22 *Daubert* Hearing Tr. at 69.

B. Analysis

The Plaintiffs failed to meet their procedural burden of establishing the reliability of their experts' methodologies because they altogether failed to argue in their Response that any of the *in vivo* studies that their experts based their endogenous formation opinions upon are reliable. *Frazier*, 387 F.3d at 1260 (explaining that the proponent of expert testimony always bears the burden of establishing the reliability of her expert's testimony). *See generally* DE 5913. Although the Plaintiffs raised arguments in support of the reliability of Matsuda and Krawczynski at oral argument, both arguments were raised in contravention of the Court's order that new arguments not be raised. *See* DE 5995. For these reasons alone, the Court agrees with the Defendants.

In the alternative, even if the Court were to consider the new arguments raised by the Plaintiffs at oral argument, the Plaintiffs mere assurances that Matsuda and Krawczynski are generally accepted studies in the scientific community are not sufficient to establish the reliability of those studies—the Court cannot simply take their word for it. *See McClain*, 401 F.3d at 1244 (explaining that an "expert's assurances that he has utilized generally accepted scientific methodology are insufficient" and that a court must do more than simply take "the expert's word for it" (alteration, internal quotation marks, and citation omitted)). Moreover, even if general acceptance of the methodologies used in these two studies was established, acceptance in the scientific community and peer review are not necessarily sufficient to establish the reliability of a scientific methodology. *See In re Deepwater Horizon*, 2020 WL 6689212, at *12 ("[The expert's] justification for not providing any independent assessment of the studies she relied on was the fact

that the studies were all peer reviewed and published. This does not cure the problem, as 'it is well established that [p]ublication . . . is not a *sine qua non* of admissibility.'" (second and third alterations in original) (quoting *Allison*, 184 F.3d at 1316)). Upon review, the methodologies employed in both Matsuda and Krawczynski have multiple problems that render both studies unreliable.

First, neither the Plaintiffs nor the Plaintiffs' experts explain how Matsuda or Krawczynski properly controlled or accounted for the diets of their participants. The authors of Matsuda stated that their participants were allowed to eat whatever they wanted, whereas the authors of Krawczynski made no mention of diet at all. Matsuda et al., *supra*, at 163. The Plaintiffs' experts opine that people can be exposed to NDMA from sources such as diet, water, and air. *See* Le Report at 10; Panigrahy Report at 141. As such, diet and drinking water are potential confounding factors that should have been accounted for by the authors in these studies. *See* Le Report at 94 ("The confounding factors of particular interest in establishing a causal inference of ranitidine to specific cancers are: dietary intake (especially for foods with high nitrate/nitrite content, vitamin C and E), smoking (due to thiocyanate content), alcohol consumption; these confounding factors affect NDMA formation either via inhibition or induction.").

Next, in both Matsuda and Krawczynski, participants were administered additional drugs simultaneously with ranitidine. In Matsuda, participants were administered anticholinergics and antacids, and in Krawczynski, participants were administered amoxicillin and nitroimidazole. Neither the Plaintiffs, the study authors, nor the Plaintiffs' experts provide an explanation as to why these additional drugs did not confound the results of the studies.

Also in Krawczynski, the researchers did not test the participants' gastric fluid until four to six weeks after treatment. The Plaintiffs' experts opine that both ranitidine and NDMA are

rapidly absorbed and metabolized by the body after oral administration. According to Dr. Le, "after oral administration, NDMA gets absorbed extensively (>90%) primarily from the lower intestinal tract, enters the blood and rapidly distributes to many organs throughout the body in a matter of minutes." Le Report at 46. Similarly, Dr. Panigrahy opines that "NDMA is absorbed very quickly, as the highest blood level of NDMA was observed at 5 minutes after administration of NDMA into the stomach and duodenum." Panigrahy Report at 82. Neither the Plaintiffs nor their experts explain how, given the pharmacokinetics of NDMA, it is reliable to measure gastric juice for endogenous formation of NDMA four to six weeks after ranitidine is administered.

Finally, the Plaintiffs' own expert explained that the results of Matsuda do not support his opinion that ranitidine uniquely forms into NDMA in the human stomach as compared to other H2-blockers. Panigrahy Dep. at 448-451. Dr. Panigrahy explained that there were many limiting factors that could have affected the results in this study, including fasting conditions, varying nitrite concentrations and pH levels among participants, and the fact that the techniques used to measure NDMA back in 1990 made it difficult to measure NDMA. *Id.* at 449-51. In summary, the considerable number of methodological flaws in Matsuda and Krawczynski renders these studies unreliable bases to support an opinion that NDMA forms endogenously from ranitidine.

In conclusion, the Plaintiffs have not met their procedural burden to explain how the *in vivo* studies their experts upon for their endogenous formation opinions are reliable; and, a substantive review of these studies indicates that these studies are not reliable for the reasons discussed above. In numerous instances, the Plaintiffs' experts have asserted methodological principles, then deviated from their own principles to rely upon studies that support their conclusions. The Plaintiffs' experts also rely upon studies that do not support their conclusions.

Neither the Plaintiffs nor their experts reconcile these inconsistencies. These factors weigh heavily against the admissibility of the Plaintiffs' experts' endogenous formation opinions.

2. *In Vitro* Studies

In addition to the *in vivo* studies, the Plaintiffs' experts also rely upon *in vitro* studies in support of their endogenous formation opinions. In these studies, ranitidine was incubated with nitrites in SGF to determine whether ranitidine and nitrites are capable of reacting to form NDMA. The experiments tested the reactions of ranitidine and nitrite at varying pH levels and nitrite concentrations. The Defendants contend that the *in vitro* studies that the Plaintiffs' experts rely upon do not constitute a reliable scientific basis for their endogenous formation opinions. These studies are described below.

a. ***In Vitro* Studies Identified by the Parties**

The Defendants highlight five *in vitro* studies: Tanner,[70] Zeng & Mitch,[71] the 2019 Valisure Citizen Petition,[72] Braunstein,[73] and Gao.[74] In their Response, the Plaintiffs note that their experts considered additional studies to inform their endogenous formation opinions, listing a number of studies as examples. *See* DE 5913 at 8-9. The Plaintiffs do not provide reasons why these studies constitute reliable evidence of endogenous formation. As such, the Court will not describe those additional studies here, but will address the Plaintiffs' experts' reliance upon them below. The Court proceeds to describe only the five studies highlighted by the Defendants.

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[70] R.J.N. Tanner et al., Glaxo Grp. Rsch. Ltd. Division of Biochemical Pharmacology, The Determination of N-nitrosodimethylamine Formed by the Reaction of Ranitidine Hydrochloride with Sodium Nitrite (April 6, 1982) (unpublished manuscript).
[71] Zeng & Mitch, *supra* note 56.
[72] Letter from Valisure to the FDA, Valisure Citizen Petition of Ranitidine (Sept. 9, 2019) [hereinafter Valisure Citizen Petition].
[73] Lior Z. Braunstein et al., *Analysis of Ranitidine-Associated N-nitrosodimethylamine Production Under Simulated Physiologic Conditions*, JAMA Network Open, Jan. 9, 2021, at 1.
[74] Zongming Gao et al., *In Vitro Analysis of N-nitrosodimethylamine (NDMA) Formation from Ranitidine Under Simulated Gastrointestinal Conditions*, Jama Network Open, June 28, 2021, at 1.

i. Tanner

The first study the Plaintiffs rely upon in support of their endogenous formation argument is Tanner. The Tanner study is an unpublished and non-peer reviewed study conducted internally by GSK to determine whether ranitidine hydrochloride and nitrite reacted in SGF to form NDMA. R.J.N. Tanner et al., Glaxo Grp. Rsch. Ltd. Division of Biochemical Pharmacology, The Determination of N-nitrosodimethylamine Formed by the Reaction of Ranitidine Hydrochloride with Sodium Nitrite 2 (April 6, 1982) (unpublished manuscript). Researchers ran two sets of incubation experiments. In the first set of experiments, researchers incubated 10 mM and 40 mM of ranitidine with 40 mM sodium nitrite. *Id.* at 2. In the second set of experiments, the researchers incubated 1 mM ranitidine with 0.3 mM sodium nitrite. *Id*. According to the study authors, this second set of experiments was intended to "simulate[] the drug and nitrite concentrations anticipated in the human stomach after ingestion of a nitrite rich meal and 150 mg ranitidine." *Id*.

For both sets of experiments, the researchers utilized gas chromatography-mass spectrometry to measure the amount of NDMA that formed in the mixtures. In the first set of experiments, the researchers reported that when 10 mM ranitidine was incubated with 40 mM sodium nitrite, 232 µg NDMA was formed, and when 40 mM ranitidine was incubated with 40 mM sodium nitrite, 219 µg NDMA was formed.[75] *Id.* at 6. For the second set of experiments, the researchers did not report the specific amount of NDMA found, stating that it "gave a low intensity signal . . . similar to that observed in the analytical record of an extract of control gastric juice incubated without [ranitidine]." *Id*. In other words, the amount of NDMA formed in 0.3 mM sodium nitrite concentration was so small that it could not be quantified.

[75] 232 µg NDMA is equivalent to 232,000 ng NDMA; 219 µg NDMA is equivalent to 219,000 ng NDMA.

ii. Zeng & Mitch

The second *in vitro* study that the Plaintiffs offer in support of their endogenous formation theory is Zeng & Mitch. Drs. Zeng and Mitch tested whether ranitidine formed NDMA when incubated with varying concentrations of sodium nitrite in SGF. Zeng & Mitch, *supra*, at 626. As noted, Zeng & Mitch was retracted in its entirety in 2021.

iii. Valisure Citizen Petition

The third study that the Plaintiffs rely upon was conducted by Valisure in support of its September 13, 2019, Citizen Petition to the FDA. In the Citizen Petition, Valisure claimed that it detected "extremely high levels" of NDMA in ranitidine. Letter from Valisure to the FDA, Valisure Citizen Petition of Ranitidine 1 (Sept. 9, 2019) [hereinafter Valisure Citizen Petition]. To support their claim, Valisure tested varying concentrations of sodium nitrite with ranitidine, incubated in SGF. In the experiment, no NDMA was detected in the control. *Id.* at 7. At 25 mM sodium nitrite condition, the researchers measured 236 ng NDMA. *Id*. At the 50 mM sodium nitrite condition, they measured 3,045 ng of NDMA. *Id*.

The Defendants challenged, during a discovery hearing held on January 19, 2022, the validity and weight[76] of Valisure's scientific findings in its Citizen Petition. *See* Jan. 19 Hearing Tr. at 42. As part of that challenge, the Defendants served a subpoena for Valisure records. To evaluate Valisure's motion to quash the subpoena, the Court asked the Plaintiffs whether they intended to rely upon the results of the Valisure study as substantive evidence to prove that ranitidine causes cancer. *Id.* at 43. The Plaintiffs represented on the record that they did not intend to rely upon the Valisure study to prove general causation and that their experts also would not

[76] The basis for the Defendants' challenge is discussed more fully in the Epidemiology Motion at docket entry 5699, page 15.

rely upon Valisure in their expert reports. *Id.*; DE 5165 at 2. Relying upon the representation, the Court quashed the subpoena in part. DE 5165 at 2-3.

Because of the Plaintiffs' prior representation to this Court and because the Court relied upon that representation to quash the Defendants' subpoena, the Plaintiffs and their experts are estopped from relying upon the Valisure study for their general causation opinions. The Plaintiffs may only refer to the Valisure study for the limited purpose of describing the history of this litigation. DE 5237 at 43-44.

iv. Braunstein

The Plaintiffs also rely upon Braunstein to support their endogenous formation claim. Braunstein is a published, peer reviewed study in which researchers added ranitidine to SGF under various pH levels and sodium nitrite concentrations. Lior Z. Braunstein et al., *Analysis of Ranitidine-Associated N-nitrosodimethylamine Production Under Simulated Physiologic Conditions*, JAMA Network Open, Jan. 9, 2021, at 1, 1. The formation of NDMA was measured using liquid chromatography-mass spectrometry ("LC-MS"). *Id*.

The lowest sodium nitrite concentration tested was 1 mM/L, and the highest tested was 50 mM/L. *Id*. The researchers measured 947 ng of NDMA in the 1 mM/L concentration of sodium nitrite, and 320,000 ng of NDMA in the 50 mM/L concentration. *Id.* at 2. The authors concluded that a pH of 2.5 and 50 mM/L sodium nitrite concentration are "optimally reactive physiologic conditions." *Id*. In a correction issued in March 2022, the authors updated the charts on page 1 to reflect measurements at sodium nitrite conditions below 1 (0, 0.01, 0.05, 0.5). *See* Brown Decl., DE 5692 Supplement 5 Ex. 47 at 1486-87. That chart represents that even at 0 mM/L sodium nitrite (in other words, no sodium nitrite was added to the SGF), the levels of NDMA detected still approached nearly 1,000 ng. *Id*.

v. Gao

Contrary to the above studies, the Plaintiffs' experts determined that Gao only "offered minimal insight" into the question of whether NDMA can form endogenously from ranitidine. DE 5913 at 10. In Gao, researchers tested the potential formation of NDMA from ranitidine under different combinations of fluid volume, pH, and nitrite concentration. Zongming Gao et al., *In Vitro Analysis of N-nitrosodimethylamine (NDMA) Formation from Ranitidine Under Simulated Gastrointestinal Conditions*, Jama Network Open, June 28, 2021, at 1, 2. The researchers also conducted a literature review of 26 clinical studies which measured gastric nitrite concentrations and pH from a variety of patient populations to create thresholds for physiologic (capable of being found in the human body) and supraphysiologic (incapable of being found in the human body) levels of nitrite. *Id.* at 2-4.

Researchers added ranitidine to SGF at varying nitrite concentrations and pH levels, then measured the amount of NDMA that formed using LC-MS. The study authors found that NDMA forms most readily in acidic conditions (pH 1.2-2.5), and so they conducted subsequent experiments in SGF at a pH of 1.2. Id. at 5. During baseline testing, the SGF at 1.2 pH with no ranitidine added had a mean of 22 ng of NDMA. *Id.* The study authors stated that 1.2 pH represented the conditions in a fasted stomach. When ranitidine was added to SGF with 100 µM/L nitrite concentration, the mean amount of NDMA measured was 21 ng. *Id.* At both 1,000 µM/L and 5,000 µM/L, the mean amount of NDMA measured was 24 ng. *Id*. Only at 10,000 µM/L, which "is approximately 18,000-fold greater than the clinically observed 95th percentile at pH levels less than 2," did the NDMA exceed the baseline amount. And even then, the amount of NDMA detected hovered slightly under 100 ng. *Id*.

When they conducted the experiment with 250 mL SGF (thought to represent a stomach after having consumed 200 mL of water), "no NDMA was detected at the upper physiologic range of gastric nitrite concentration (100 μM/L) or 10-fold physiologic (1,000 μM/L) nitrite concentrations" at any pH. *Id.* at 5. With 250 mL SGF, NDMA was detected only at the supraphysiologic 5,000 μM/L and 10,000 μM/L conditions. *Id.* at 5-6. Regarding the detection of NDMA at 5,000 μM/L, the authors stated:

> [T]his scenario is unlikely to be encountered in patients, as consuming water will increase pH and decrease the gastric nitrite concentration by dilution. Furthermore, 5,000 μM/L is approximately 600-fold greater than the 95th percentile of gastric nitrite at pH values of less than 2 from patients with 24-hour (combined fed and fasted) gastric fluid measurements.

Id. at 6. The authors concluded that "this in vitro study suggest[s] that ranitidine does not convert to NDMA in the human stomach or small intestine under physiological conditions." *Id.*

b. **Plaintiffs' Experts' Reliance on the *In Vitro* Studies**

The Defendants make two arguments as to why the *in vitro* studies that the Plaintiffs' experts rely upon do not constitute a reliable scientific basis for their endogenous formation opinions. First, the Defendants argue that the Plaintiffs' experts employed unreliable methodologies to review and weigh the *in vitro* studies. DE 5696 at 7, 16-18. Specifically, the Defendants argue that the Plaintiffs' experts' reasons for disregarding Gao are internally inconsistent and based on studies that do not support the experts' conclusions. DE 5960 at 6, 11. Second, the Defendants argue that the *in vitro* studies are unreliable because they are not "physiologically relevant." DE 5696 at 13. These two arguments and the Plaintiffs' responses are discussed below.

i. Plaintiffs' Experts' Methodologies for Weighing the *In Vitro* Studies

A. Parties' Arguments

First, the Defendants argue that the Plaintiffs' experts' methodologies for weighing the *in vitro* studies are unreliable and inconsistent. In response, according to the Plaintiffs, their experts properly weigh Gao because "the Gao study offered minimal insight on endogenous NDMA formation with ranitidine use." DE 5913 at 10. Drs. Marletta, Michaels, Panigrahy, Le, and Najafi each criticize Gao. First, the Plaintiffs' experts criticize Gao because the study did not account for "numerous variables that can exist in a human stomach." Najafi Report at 84. These variables include conditions of a human stomach after a large acidic meal, obese people with a larger stomach capacity, or a nitrite-rich meal. *Id.*; Le Report at 39; Le Dep. at 321. Next, the Plaintiffs' experts criticize Gao because the study utilized data from healthy subjects. Marletta Dep. at 219; Najafi Report at 85. They also criticize Gao because the literature sources supporting the study are old and based on inaccurate analytical methods. *See* Najafi Report at 84; Marletta Dep. at 219. Finally, the Plaintiffs' experts criticize Gao because it "did not account for the chronic ingestion of ranitidine." Le Report at 39.

Stated differently, the Plaintiffs argue that their experts properly weigh Gao because the study "[did] not reflect all aspects of human physiology;" it "did not include gastric conditions in the presence of a meal;" it did not account for "typical stomach conditions expected with ranitidine use" such as eating a large acidic meal, the larger stomachs of obese individuals, or the consumption of a meal rich in processed nitrites; and its supporting literature was flawed and was

conducted under fasting conditions. DE 5913 at 8, n.13, 10, 10 n.25 (alteration in original) (quoting Gao et al., *supra*, at 8).[77]

B. Analysis

The Plaintiffs' experts' applications of the weight-of-the-evidence methodologies to weigh the *in vitro* studies suffer from the same shortcomings as their methodologies to weigh the *in vivo* studies. None of the Plaintiffs' endogenous formation experts have "describe[d] each step in the process by which [they] gathered and assessed the relevant scientific evidence." *Abilify*, 299 F. Supp. 3d at 1311. This deficiency limits the Court's ability to assess the reliability of the experts' weight-of-the-evidence methodologies and, thus, weighs strongly against admissibility of the experts' endogenous formation opinions.

Next, the Court considers whether the Plaintiffs' experts also apply internally inconsistent reasons for discounting Gao while assigning stronger weight to studies that support their conclusions. First, for example, the Plaintiffs argue that they could not rely upon Gao because it did not account for "typical stomach conditions expected with ranitidine use" such as eating a large acidic meal, the larger stomachs of obese individuals, or consumption of a meal rich in processed nitrites. DE 5913 at 10. Yet, the Court could not identify any analysis in which the Plaintiffs' experts explain where they accounted for such factors in the other *in vitro* studies. The Plaintiffs' own expert, Dr. Le, stated, "I just don't think there's been *any* well-conducted studies at this point that would inform me that what's happening in an actual patient on ranitidine." Le Dep. at 317 (emphasis added).

[77] The Plaintiffs repeat an argument that they made for *in vivo* studies about the limited role of the Court in evaluating a weight-of-the-evidence methodology. They argue that the Defendants have inappropriately asked the Court to weigh the *in vitro* studies and to judge causation based exclusively upon the *in vitro* studies. DE 5913 at 21-22.

Next, the Plaintiffs' experts reject Gao because the studies that the authors relied upon were conducted under human fasting conditions. DE 5913 at 10. But the Plaintiffs' experts relied upon Matsuda, a study in which ranitidine was administered under fasting conditions. *See supra* Section V(B)(1)(a)(iii). Finally, the Plaintiffs' experts also criticize Gao because it "[did] not reflect all aspects of human physiology." DE 5913 at 10 (alteration in original) (quoting Gao et al., *supra*, at 8). But again, the Plaintiffs' experts fail to explain whether the studies they rely upon reflect all aspects of human physiology; and, in fact, they state that there are many variables that affect human physiology, and it would be "foolish" to "attempt to define a single physiologically relevant condition." *Id.* at 5-6. A well-conducted scientific experiment only changes one variable at a time. *See Reference Manual on Scientific Evidence*, *supra*, at 219-220.

ii. Physiological Relevance of the *In Vitro* Studies

A. Parties' Arguments

The Defendants second argument as to why the *in vitro* studies that the Plaintiffs' experts rely upon are unreliable is that the *in vitro* studies are not "physiologically relevant," meaning that they do not predict what happens in the human body. DE 5696 at 13-14. The Defendants claim that, in the *in vitro* studies, NDMA only formed at sodium nitrite levels "far in excess" of the upper range found in human stomachs. *Id*. at 14. According to the Defendants, the Plaintiffs' experts failed to opine on the level of nitrite in the human stomach that is physiologically relevant. *Id*.

The Plaintiffs respond that there is no such thing as a single physiologically relevant condition. DE 5913 at 5-6. They explain that several different variables, including diet, bacteria content of the stomach, inflammation, pH, volume of gastric fluid, and thiocyanate levels control the amount of nitrite found in the stomach. *Id.* The Plaintiffs further assert that the Defendants' argument that the sodium nitrite levels used in the *in vitro* studies are "too high and not

'physiological'" misses the "key point," which is that the *in vitro* studies "are designed to determine a drug's capability to nitrosate." *Id.* at 11. Finally, the Plaintiffs emphasize that they rely on other *in vitro* evidence in addition to the studies highlighted by Defendants. *Id.* at 8.

B. Analysis

As with their *in vivo* studies, the Plaintiffs do not meet their burden to show that their *in vitro* studies are reliable because they failed to argue in their Response that *any* of the *in vitro* studies that formed the basis for their endogenous formation opinions upon are reliable. *Frazier*, 387 F.3d at 1260. Setting aside the lack of a response, experts seeking to rely upon *in vitro* studies must explain "how the *in vitro* data can be reliably extrapolated to predict a drug's effects in humans." *In re Abilify*, 299 F. Supp. 3d at 1310.

An extrapolation is an inference or estimation a researcher makes when drawing a conclusion about a value that has not been measured based on another value that *has* been measured. Because *in vitro* data is derived in a laboratory setting from experiments conducted on cells and tissues outside of the human body, any conclusion made about humans based on *in vitro* data necessarily requires an inferential step. Experts must be able to explain that inferential step to satisfy the helpfulness and reliability prongs of *Daubert*. *See Allison*, 184 F.3d at 1312 (explaining that helpful testimony must "fit" the facts of the case, meaning it must have "a valid scientific connection to the pertinent inquiry" (quoting *Daubert*, 509 U.S. at 591)).

The key inquiry here is whether the Plaintiffs' experts have explained how and why the results of the *in vitro* studies "transfer to a live human" and whether they have accounted for the "factors that might allow [them] to make such an extrapolation." *See In re Denture Cream Prods Liab. Litig.*, 2015 WL 392021, at *12; *Reference Manual on Scientific Evidence*, *supra*, at 223 ("Confidence in the appropriateness of an extrapolation cannot come from the experiment itself.

It comes from knowledge about outside factors that would or would not affect the outcome."). The extrapolation requirement is not met simply because an expert puts forward an explanation. District courts are within their discretion to find an expert's explanation inadequate. *See Allison*, 184 F.3d at 1313-14.

The Plaintiffs' experts have not sufficiently explained how they can reliably extrapolate from the *in vitro* studies on ranitidine nitrosation to their conclusion that ranitidine can transform into NDMA in the human digestive tract. Although the Plaintiffs argue that the *in vitro* studies were designed to simply determine a drug's capability to nitrosate, *see* DE 5913 at 11, an expert may not rely upon even a reliable, well-conducted scientific study where the expert offering it cannot explain the link between the study and the facts of the case. *See Quiet Tech.*, 326 F.3d at 1347-48 (emphasis omitted) (quoting *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 743 (3d Cir. 1994)). Regardless of whether the Plaintiffs' *in vitro* studies demonstrate ranitidine's ability to nitrosate, the Plaintiffs' experts have not established that these studies demonstrate ranitidine's ability to nitrosate *in humans*.

The Defendants identify nitrite concentration as a factor that should be accounted for in extrapolating from the *in vitro* studies to humans. DE 5696 at 13-14. Sodium nitrite plays a significant role in these studies. The Plaintiffs' experts' studies tested ranitidine at various sodium nitrite concentrations ranging from 0.3 mM/L up to 50 mM/L (3,000 μM/L to 50,000 μM/L). The Plaintiffs' experts conclude that the transformation of ranitidine into NDMA in the stomach is dependent in part on the amount of sodium nitrite present. *See* Le Report at 38; Marletta Report at 42; Michaels at 49.

However, according to the Plaintiffs' own experts, not all of the nitrite concentrations tested are capable of being found in the human stomach. Dr. Panigrahy acknowledged at his

deposition that the 71 mM/L nitrite concentration tested in De Flora,[78] which he relied upon in forming his opinion that ranitidine can form endogenously, is "about 20,000 times that likely to be expected in fasting human [gastric] juice" and "300 times that after a nitrite-rich meal" and that such a level of nitrite would be "an unrealistic situation in the human stomach." Panigrahy Dep. 425-29. He further acknowledged that a human would die with a nitrite concentration that high. Panigrahy Dep. 422. This fact underscores the importance of understanding the relevance to humans of the nitrite concentrations tested in the *in vitro* studies.[79]

The Defendants asked the Plaintiffs' experts at deposition many times to explain how the amounts of nitrite tested in the *in vitro* studies relate to the levels of nitrite found in the human stomach. *See, e.g.*, Le Dep. at 310, 316, 336-37. The experts did not provide an explanation. They responded that it would either be too difficult or impossible to extrapolate or to provide any biologically plausible values for nitrite in the human stomach. For example, when asked to identify any study that shows that more than 0.1 millimolar of nitrite can be found in a human stomach, Dr. Le stated "You know, something early in my career that I've learned related to this is, just because you don't have data doesn't mean there's an absence of that." Le Dep. at 321. Similarly, Dr. Marletta stated that "because there are all these other variables . . . the size of your stomach, what you ate, all of those kinds of things, that could be enough nitrite to drive nitrosamine formation. We simply cannot draw a line from those in vitro experiments directly to a physiological experiment. It's just too complicated." Marletta Dep. at 224. When asked

[78] S. De Flora, *Cimetidine, Ranitidine, and Their Mutagenic Nitroso Derivatives*, 2 Lancet 993 (1981).

[79] The parties' briefing and questioning at depositions make clear that the maximum amount of nitrite that possibly can be found in a human stomach is a disputed fact in this litigation. *See* Marletta Dep. at 219-20. *Compare* DE 5696 at 14, *with* DE 5913 at 9-10. The Court does not attempt to resolve this factual question, nor does it require that the Plaintiffs settle on a threshold amount of sodium nitrite that is physiologically possible in humans. However, the Plaintiffs are required to explain why they can reliably infer that ranitidine can transform into NDMA in a human stomach based on the observed formation of NDMA from ranitidine at the amounts of nitrite tested in the *in vitro* studies. The Plaintiffs' experts have failed to do so.

specifically whether the nitrite concentrations tested in Tanner are physiologically relevant, Dr. Marletta stated, "The issue of physiological relevance is probably the—some of the most complicated torturous aspects to discuss." *Id.* at 206.

At oral argument, the Court asked the Plaintiffs to "provide a range of nitrate[80] levels that would be realistic to find in the human stomach." Defendants' Sept. 22 *Daubert* Hearing Tr. at 60. The Plaintiffs did not answer the question, and so the Court then asked: "Is there a level of sodium nitrite that would be toxic to humans that has been established by anyone, per the Plaintiffs' position?" The Plaintiffs' responded, "I don't believe we have discussed the toxicity of nitrite." *Id.* at 61. The Plaintiffs asserted that the levels of nitrite found in the stomach are the same as those found in Dr. Najafi's SGF testing. *Id.*; *see supra* Section V(A)(1)(g)(ii) (wherein the Court excluded Dr. Najafi's expert opinion).

The Plaintiffs further argue that human physiologic conditions cannot be defined due to the number of variables that can affect the amount of nitrite in human stomachs:

> [E]ndogeneity is not informed by one variable alone—or one set of "actual human physiological conditions" as Defendants unusually assert, despite the established body of scientific literature to the contrary. Rather, numerous variables exist that affect the amount of nitrites in the stomach, including diet, bacterial content of the stomach, inflammation, pH, volume of gastric fluid and thiocyanate levels. To attempt to define a single physiologically relevant condition is foolish at best.

DE 5913 at 5 (footnotes omitted). While the amount of nitrite in an individual person's stomach may be affected by numerous variables, this fact does not relieve the Plaintiffs of their burden to explain the inferential leap that their experts make from the *in vitro* studies to humans. Neither the Plaintiffs nor their experts explain how the variables that affect human nitrite levels were accounted for in the studies or how they relate to the amount of nitrite that can be found in the

[80] The Court and the parties occasionally, and perhaps mistakenly, used the words "nitrate" and "nitrite" interchangeably at oral argument.

human stomach. For example, Dr. Michaels stated generally in his report that in the Braunstein study, "NDMA formation from ranitidine was found across a range of physiologically relevant conditions, with both increasing nitrite and decreasing pH," without any further explanation. Michaels Rpt. at 48. This explanation is insufficient. The Plaintiffs' failure to provide an extrapolation explanation means that "there is simply too great an analytical gap between the data and the opinion proffered." *Chapman*, 766 F.3d at 1305-06 (quoting *Hendrix II*, 609 F.3d at 1194).

After a review of the totality of the evidence, the Court concludes that the Plaintiffs have not met their burden to show that their experts used reliable methodologies to reach their conclusions that NDMA can form endogenously from ranitidine. The Plaintiffs also did not meet their burden to explain how their experts extrapolated from *in vitro* data to conclude that ranitidine transforms endogenously into NDMA in humans. As such, all of the Plaintiffs' experts are precluded from opining that NDMA can transform endogenously from ranitidine.

C. Conclusion on the Amount of NDMA in Ranitidine

For all of the foregoing reasons, Dr. Najafi's testing of ranitidine is unreliable, and the Plaintiffs' expert opinions on endogenous formation evidence are also unreliable. When an expert, in forming his or her expert opinion, relies upon an unreliable expert opinion, their expert opinion is also unreliable. *See In re Abilify*, 299 F. Supp. 3d at 1311-12; *see also supra* Section VI(B). Drs. Le, McTiernan, Moorman, Panigrahy, and Salmon relied upon Dr. Najafi's opinion to opine on the amount of NDMA found in ranitidine. Additionally, Drs. Panigrahy, Michaels, Marletta, Le, and Najafi relied upon unreliable *in vivo* and *in vitro* studies to opine on the endogenous formation of NDMA. Consequently, for these reasons, and in consideration of the totality of the evidence, the Court excludes the above-referenced experts to the extent that they rely upon Dr. Najafi's testing or the external testing for the endogenous formation of NDMA.

The Defendants do not challenge the reliability of the FDA's testing as to the amount of NDMA found in ranitidine. Also, naturally, the Defendants do not challenge the reliability of their own testing. Because the Court has excluded the Plaintiffs' experts who opined on the amount of NDMA in ranitidine (in Sections V(A) and (B), *supra*), the Plaintiffs are left with no reliable evidence as to the amount of NDMA other than the FDA's testing and the Defendants' own testing.

The Court's discussion of the amount of NDMA in ranitidine is therefore complete,[81] and the Court turns to a different question: Given the amount of NDMA in ranitidine as detected by the FDA and the Defendants, do the Plaintiffs have reliable evidence that ranitidine could have caused any Plaintiffs' cancer? To answer this question, the Court must categorize the Plaintiffs' additional general causation evidence. Some of the additional evidence, pursuant to Eleventh Circuit case law, is "primary" evidence, and some if it is "secondary" evidence. The definition of primary evidence and secondary evidence is the subject to which the Court now turns.

VI. Primary Evidence of General Causation

In the Eleventh Circuit, courts must consider the different categories of scientific evidence that an expert has relied upon in forming a general causation opinion in a toxic tort case. *See In re Abilify*, 299 F. Supp. 3d at 1306; *see also Chapman*, 766 F.3d at 1308. A general causation expert must rely on at least one of three "primary" types of evidence for his or her opinion to be considered reliable. *In re Abilify*, 299 F. Supp. 3d at 1306; *see also Chapman*, 766 F.3d at 1308. These "primary" categories of evidence are epidemiology, dose-response relationship, and background risk of disease. *Chapman*, 766 F.3d at 1308. Epidemiology studies diseases in human populations through experimental and observational studies that measure the effects of exposure to an agent

[81] The Court's ruling on the amount of NDMA in ranitidine factors into its analysis of dietary and occupational epidemiology, and it also factors into its analysis of the Plaintiffs' evidence of dose response. *See infra* Sections VI(A)(3)(b)(iii), VI(B).

on humans. *In re Abilify*, 299 F. Supp. 3d at 1306-07. Dose-response describes how changes in the amount, intensity, or duration of exposure to an agent affects the risk of disease, either by increasing or decreasing that risk. *Id.* at 1307. And background risk of disease is the risk that the plaintiffs and others in their community have of developing the disease *without* exposure to the agent of interest. *Id.* at 1307-08. An expert opinion lacking support of one of these three types of primary evidence is unreliable as a matter of law and cannot prove general causation. *Id.* at 1306; *Chapman*, 766 F.3d at 1308.

A general causation expert may also rely upon "secondary" evidence. Secondary evidence is evidence that cannot *alone* prove general causation, even in the aggregate. *In re Abilify*, 299 F. Supp. 3d at 1306. Secondary evidence includes mechanistic/biological plausibility evidence, animal studies, *in vitro* studies, and extrapolations from analogous drugs. *See id.*; *see also Chapman*, 766 F.3d at 1308. Although secondary evidence cannot prove general causation by itself, an expert may rely upon it in conjunction with primary evidence "as confirmatory pieces of the totality of the evidence." *See In re Seroquel Prods. Liab. Litig.*, No. 6:06-MD-1769-ORL-22D, 2009 WL 3806435, at *8 (M.D. Fla. June 23, 2009).

The Court reviews and analyzes the primary evidence that the Plaintiffs' experts relied upon in forming their general causation opinions. Each type of primary evidence—epidemiology, dose-response relationship, and background risk of disease—is addressed below in subsections A through C. In subsection D, the Court will render its overall conclusions regarding the admissibility of the Plaintiffs' experts' opinions under *Daubert*. Then, the Court proceeds to address the Plaintiffs' experts' secondary evidence.

A. Epidemiology

The first type of "primary" evidence in the Eleventh Circuit is epidemiology. Five of the Plaintiffs' experts rely upon epidemiological studies to opine that ranitidine can cause the five Designated Cancers: Drs. McTiernan, Moorman, Salmon, Michaels, and Le. The epidemiological studies that they discuss in their reports can be grouped into two general categories. The first category is referred to as "ranitidine studies." In the ranitidine studies, epidemiologists study what effect ranitidine consumption may or may not have on human populations. The second category of studies may be labeled "non-ranitidine studies." The non-ranitidine studies consist of dietary studies and occupational studies. In the dietary studies, epidemiologists study what effect specific foods may or may not have on those who ingest large quantities of the foods being studied. In the occupational studies, epidemiologists study what effect certain occupations have on those who work in the occupation.

A certain amount of background information on epidemiology is helpful for an understanding of the Court's discussion and analysis of the Epidemiology Motion. Accordingly, the Court (1) sets forth a brief summary of key epidemiological concepts. Next, the Court (2) summarizes the parties' competing positions on epidemiology before turning to (3) the Defendants' generalized challenges to the Plaintiffs' epidemiological experts. Finally, the Court analyzes (4) the Defendants' expert-specific challenges, and (5) rules on the Epidemiology Motion.

1. Summary of Epidemiological Concepts

In this section, the Court summarizes the key scientific concepts that form the basis of the Defendants' Epidemiology Motion, the Plaintiffs' Response, and the Court's ultimate analysis. To that end, the Court sets forth below a general summary of what epidemiology is, how

epidemiological studies are analyzed, and how some of the ranitidine epidemiological studies in this MDL were conducted.

a. **Epidemiology, Generally**

Epidemiology is the field of public health and medicine that studies the incidence, distribution, and etiology of disease in human populations.[82] The purpose of epidemiology is to better understand disease causation and to prevent disease in groups of individuals. Epidemiological evidence consists of experimental and observational studies, with experimental studies generally providing stronger evidence than observational studies because of the level of control that a researcher may exert over the conditions of an experimental study.

For experimental evidence, the "gold standard" is the randomized trial, or clinical trial. In a clinical trial, subjects are randomly assigned either to a group exposed to the agent of interest or to an unexposed group and are then evaluated over time for the development of the disease. However, clinical trials are often unavailable in toxic tort cases because it is unethical to randomly assign a human a potentially harmful dose of a suspected toxin. Here, in this MDL, there is one randomized clinical trial on the potential of ranitidine to degrade into NDMA, the Florian study. The Court examined the Florian study in detail in Section V(B)(1), *supra*.

For observational evidence, there are two primary types of observational evidence: cohort studies and case-control studies. In cohort studies, researchers measure and compare the incidence of disease in exposed and unexposed groups, while in case-control studies researchers measure and compare the frequency of exposure in a group with the disease and a group without the disease.

[82] The Court's draws upon the epidemiology section on the Reference Manual on Scientific Evidence, Third Edition, published by the Federal Judicial Center in 2011. The Eleventh Circuit routinely cites the reference manual when considering causation. *E.g., McClain*, 401 F.3d at 1239; *Frazier*, 387 F.3d at 1261 n.14. In the interest of readability, the Court does not cite the Reference Manual each time it sets forth a concept discussed therein. Suffice it to say there is an abundance of case law supporting the Court's summary of epidemiology.

Unlike experimental studies in which subjects are randomly assigned to exposed and placebo groups, observational studies are subject to bias due to the possibility of differences between study populations.

In this MDL, there are many observational studies on ranitidine, each of which is discussed in this Order. In analyzing these studies, it is important to remember that epidemiology assumes that the disease (here, cancer) is not distributed randomly in a group of individuals and that persons who are exposed to the agent in question (here, ranitidine) can be identified. Ultimately, the core goal of epidemiological studies in this MDL is to estimate the increased or decreased risk of developing cancer if someone consumed ranitidine. How that risk is measured is the next topic of discussion.

b. **Measuring Increased Risk**

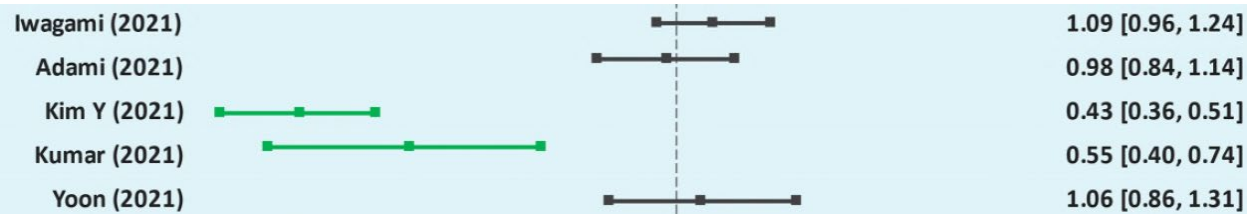
An increased risk of developing a disease is typically measured through an "odds ratio" or a "relative risk ratio."[83] An odds ratio greater than 1.0 suggests that, when a subject develops a disease or condition, the subject is more likely to have been exposed to the substance of interest. Similarly, a relative risk ratio greater than 1.0 means that a group exposed to a particular agent was more likely to develop a particular disease. By way of example, a relative risk ratio of 1.2 indicates that a group of persons (who were exposed to the agent of interest) had a 20% increased risk of developing a particular disease, when that group was compared to a group of persons who were not exposed to the agent of interest. Conversely, a ratio of less than 1.0 indicates that the agent of interest has a protective effect and reduces the chance of developing a particular disease. A ratio

[83] Although there are differences in how these ratios are computed, the differences are not relevant to the Court's general causation inquiry. In the interest of simplifying the discussion, the Court may occasionally reference these two ratios as being more or less interchangeable.

by itself, however, does not fully communicate an epidemiologist's conclusions because an epidemiologist must consider whether the measured ratio was a result of randomness or chance.

c. **Confidence Intervals**

To account for randomness and chance, odds ratios and relative risk ratios are typically reported with an accompanying statistical "confidence interval." A 95% confidence interval, which is considered by statisticians to be a commonly used confidence interval, represents a range of ratios that, at least 95% of the time, capture the true risk ratio. To illustrate this principle, a relative risk ratio of 1.2 could be accompanied with a 95% confidence interval of 1.1 to 1.3. This means that an epidemiologist is confident that, once randomness and chance are taken into account in a study's recorded results, the true relative risk of a particular agent is somewhere between 1.1 and 1.3, at least 95% of the time. The following visual example of confidence intervals is taken from Appendix C of the Defendants' Epidemiology Motion:



DE 5736 at 112. Using the first study (Iwagami) as a demonstrative, the study author concludes that the relative risk of people who consume ranitidine, as opposed to people who consume an alternative drug to ranitidine, is 1.09, indicating a 9% increased risk of developing the disease of interest, cancer. This 1.09 ratio is accompanied with a confidence interval of .96 to 1.24, indicating that the study author is 95% confident that, once randomness and chance are taken into account, the relative risk of ranitidine use is somewhere between .96 and 1.24. Because the visual depiction of the confidence interval in this study crosses the dotted line in the middle of the graph, however,

further discussion of the study is necessary as it demonstrates the problem of statistical significance.

d. **Confidence Intervals, Risk Rates of 1.0, and Statistical Significance**

The dotted line indicates a risk ratio of 1.0, akin to a finding that there is no association whatsoever between ranitidine and cancer. When a confidence interval spans 1.0—when it extends both to the left and to the right of 1.0—this is not typically considered (within the scientific community) to be a statistically significant finding. Stated differently, the study author cannot conclude with 95% confidence (the usual confidence rate) whether ranitidine actually confers a *protective effect* on the user—the part of the confidence interval to the left of the dotted line—or a *detrimental effect* on the user—the part of the confidence interval to the right of the line. This uncertainty means, at least as a general matter, that the study finding is not helpful to a causation inquiry.

For a ratio to generally be helpful in a causation inquiry it must be statistically significant—it must exist completely and fully to the right or to the left of the dotted line—and it must not include 1.0 in its confidence interval. *See Reference Manual on Scientific Evidence*, *supra*, at 573; *Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 887 (10th Cir. 2005); *c.f. Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194, 1198 (11th Cir. 2002) (noting that the parties did not present studies with statistically significant results and the epidemiological evidence was inconclusive). Even a statistically significant finding, however, may still be unhelpful to a causation inquiry if the measured association has no real bearing on causation, as explained below.

e. **Association and Causation**

Using an example from the Reference Manual on Epidemiology, there is a statistically significant confidence interval comparing hair color to the risk of death. Those with gray hair, as

a group, are positively associated with a higher risk of death as opposed to other hair colors. Yet no one believes that the color of one's hair causes adverse health consequences. This is an example of a statistically significant association that is not demonstrative of causation. The lurking variable that would truly be associated with risk of death is, of course, advancing age; those of greater age merely tend to have gray hair. In this example, age is what is known as a confounder.

f. **Confounding**

Confounding arises when a factor not accounted for by a study wholly or partially explains an apparent association. For a factor to be a confounder, it must independently relate to both the variable being tested (such as hair color) and the result being measured (such as the risk of death). In the example above, age was a confounder because it is independently related to both hair color and risk of death. If a study fails to control for confounding variables, the results of the study may be skewed and produce an association where none exists or otherwise misreport the association. Thus, for an epidemiologal study to generally be reliable, it must account for confounding variables. Confounding is a particularly important topic in this MDL because of the characteristics of the typical Plaintiff, the typical consumer of ranitidine.

g. **Confounding, Ranitidine, and Cancer**

As will be explained in greater detail in the Court's analysis of the Defendants' Epidemiology Motion, there are a number of factors that are independently related to both ranitidine use and cancer. The purpose of ranitidine is to alleviate heartburn. Those who suffer from chronic heartburn and therefore regularly and systemically consume ranitidine, the Plaintiffs in this case, are positively associated with obesity, smoking, alcohol use, diets rich in fat, and certain medical conditions such as Barrett's esophagus. *See infra* Section VI(A)(4)(b). Those same factors—obesity, smoking, alcohol use, diets rich in fat, and Barrett's esophagus—are also

independently associated with a positive increase in the risk of cancer. Thus, if these confounding variables are not accounted for, they will affect the results of an epidemiological study. Almost every epidemiological study on ranitidine in this MDL attempted to test for the confounding variables listed above through an active comparator analysis.

h. **Active Comparators**

In an active comparator analysis, people who use ranitidine are compared to a similar group of people. Because ranitidine treats heartburn, and because the Plaintiffs suffer from chronic heartburn, almost all of the ranitidine epidemiological studies in this MDL compared people who take ranitidine for chronic heartburn to people who take ranitidine competitors' products for chronic heartburn. The reasoning for this comparison is that both groups of people have similar characteristics for obesity rates, diet, etc. As a result of these similarities, the thinking goes, the confounding variables are at least partially eliminated, and the relative risk of ranitidine use may be computed more accurately.

i. **Follow-Up Time**

Confounding is not the only factor that epidemiologists must consider; they must also consider whether a particular study lends itself to bias in the results. Another potential bias at the heart of the Epidemiology Motion and Response is that of follow-up bias. In most of the epidemiological studies in this MDL, people exposed to ranitidine (or NDMA) were "followed" for a number of years to see if they developed cancer. The length of time that people could be followed was limited by the data that gave rise to a particular study, with some studies able to follow participants only for a shorter time and other studies following participants for a longer time. If follow-up time is too short, then persons who would have developed cancer (had they been followed longer) are not counted and, as a result, the reported risk of cancer is lower than it

otherwise should have been. Conversely, if follow-up time is long, other factors besides what is being observed (ranitidine or NDMA) may be the reason cancer ultimately developed and, as a result, the reported risk of cancer could be higher than it otherwise should have been.

j. **Bradford Hill**

Because of the potential for data to show associations through confounding or through random chance, epidemiologists must evaluate data to decide whether an observed association is from chance, from confounding, or from a causal relationship. To accomplish this, epidemiologists often rely upon a framework called the "Bradford Hill criteria." Broadly, these criteria are: temporality (how long did the disease take to develop after exposure); the strength of the association (how high or low is the risk); dose response (does a greater dose show greater risk); replication (have a study's findings been replicated in different populations); biological plausibility (is there a sound biological reason for the findings); alternative explanations for the findings; cessation (does a cessation of exposure reduce the risk); specificity (can the exposure be traced to specific diseases); and are the results consistent with all other relevant knowledge. After considering the Bradford Hill factors, epidemiologists determine whether there is a causal relationship between what is under study—here, ranitidine—and the relevant disease—here, cancer.

2. Summary of Parties' Arguments

Turning to the Epidemiology Motion, the Defendants bring generalized challenges against all of the Plaintiffs' epidemiological general causation experts, which the Court addresses in Subsection 3, *infra*. The Defendants also bring specific, targeted challenges against individual experts, which the Court addresses in Subsection 4, *infra*. At issue in each of the Defendants'

challenges is the Plaintiffs' experts' opinion that ranitidine causes the Designated Cancers: bladder, esophageal, liver, stomach, and pancreatic cancers.

The Court will summarize the parties' expert-specific arguments in its expert-specific discussion, but the Defendants' broader, more generalized challenges can be succinctly described as follows. First, the Defendants argue that the Plaintiffs' experts' general causation conclusions and methodologies are not generally accepted in the scientific community. *See infra* Section VI(A)(3)(a). In making this argument, the Defendants cite to ranitidine epidemiological studies, pointing out that no scientist outside of this litigation has concluded that ranitidine can cause cancer. In response, the Plaintiffs argue that the scientific community's acceptance of their experts' *conclusions* are not relevant to a *Daubert* inquiry and that their experts' *methodologies* do have general acceptance in the scientific community. Second, the Defendants argue that the Plaintiffs' experts failed to apply a reliable methodology to weigh and evaluate all available data. *See infra* Section VI(A)(3)(b). The essence of the Defendants' argument on this point is that, in lieu of reliance on studies that focused on ranitidine, the Plaintiffs' experts chose to rely (for the most part) upon studies that focused on the consumption of processed meats (dietary studies) and the inhalation of rubber factory fumes (occupational studies). For their part, the Plaintiffs argue that the data their experts relied upon was part of a reliable methodology.

3. Defendants' Generalized Challenges to Plaintiffs' Epidemiology Experts

Each of the Defendants' generalized challenges is addressed in turn. To the extent concrete examples are necessary to discuss and consider the Defendants' generalized arguments, the Court references the opinions of Dr. McTiernan or Dr. Moorman, the Plaintiffs' primary epidemiological experts.

a. **General Acceptance of Plaintiffs' Experts' Conclusions and Methodologies**

In response to the Defendants' argument that the Plaintiffs' experts' opinions lack general acceptance in the independent scientific community, the Plaintiffs argue that this Court may not consider the general acceptance of their experts' conclusions—only the general acceptance of their experts' methodologies. The Plaintiffs are incorrect. By way of example, the Advisory Committee Notes to Rule 702 read as follows: "When an expert purports to apply principles and methods in accordance with professional standards, and yet reaches a conclusion that other experts in the field would not reach, the trial court may fairly suspect that the principles and methods have not been faithfully applied."

As explained by the Supreme Court in a post-*Daubert* decision, "conclusions and methodology are not entirely distinct from one another." *Joiner*, 522 U.S. at 146. The distinction between conclusions and methodology blurs when experts "extrapolate from existing data" to reach a conclusion, but an extrapolation is akin to a leap over "an analytical gap." *Id.* When the gap is too great—when the leap is too far—a court may exclude an expert's opinion. *Id.* Thus, if an expert makes an analytical leap from available data that no other scientist outside of the litigation has made, a court may consider that fact. *See id*; *see also In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig. (No. II)* (*Mirena II*), 341 F. Supp. 3d 213, 268 (S.D.N.Y. 2018) (finding that when an expert's theory "lacks any acceptance, let alone general acceptance, in the scientific community" it is an indication of an unreliable methodology), *aff'd*, 982 F.3d 113 (2d Cir. 2020). To be sure, a court's *focus* under *Daubert* is on methodologies—not conclusions. *Daubert*, 509 U.S. at 595. But for all of the reasons set forth above, the general acceptance of an expert's conclusions in the scientific community may nonetheless be considered, along with other factors, as part of a *Daubert* analysis.

Because ranitidine, an immensely successful and popular drug, has been consumed by the public for almost forty years, and because ranitidine has been sold for much of that time as an over-the-counter drug, the public health consequences, if ranitidine causes cancer, would be significant. Given that risk to the public health, it is unsurprising that the FDA's initiation of a voluntary recall of ranitidine in the spring of 2020 resulted in 10 epidemiological studies[84] that investigated the link between ranitidine and cancer.

None of those studies, according to the Defendants, concluded that there was evidence of an association—let alone causation—between ranitidine and cancer. This assertion by the Defendants, if true, is a factor in favor of exclusion because it means that the Plaintiffs' experts stand alone with their opinions, bereft of support from the scientific community at large, and it also means that no scientist has extrapolated from the existing data as the Plaintiffs' experts do. The Court therefore briefly summarizes the 10 epidemiological studies on ranitidine, as well as governmental findings on ranitidine, to determine whether there is any independent researcher or governmental body that agrees with the Plaintiffs' experts' opinions.

First, the Court summarizes the 10 epidemiological studies on ranitidine.[85]

Iwagami. Researchers analyzed data on ranitidine users from a Japanese medical data center claims database, studying a total of 600,321 individuals and many different types of cancer. Masai Iwagami et al., *Risk of Cancer in Association with Ranitidine and Nizatidine vs Other H2 Blockers: Analysis of the Japan Medical Data Center Claims Database 2005-2018*, Drug Safety,

[84] Some studies were commissioned earlier when the FDA began to investigate ranitidine. Additionally, the parties occasionally reference an eleventh study (Michaud), but the Plaintiffs' experts do not rely upon that study because it lumped ranitidine and other drugs together. McTiernan Dep. at 566-67. As the Court need not address studies that do not form a basis for the Plaintiffs' experts' opinions, it has not done so here.

[85] After the *Daubert* briefing concluded and the Court heard oral argument on the Defendants' *Daubert* Motions, the Court granted the Plaintiffs leave to file supplemental expert reports on a study that was published after oral argument, the Wang study. The Court addresses the supplemental expert reports and the Wang study in Section VI(A)(4)(c), *infra*.

Nov. 27, 2020, at 1, 4. Releasing their results in November of 2020, the researchers concluded: "[W]e found no evidence of an increased risk of cancer diagnosis in people receiving ranitidine and nizatidine compared with people receiving other H2-blockers. . . . Thus, we conducted the current study and demonstrated for the first time (to our knowledge) that there is no significant association between ranitidine/nizatidine and the incidence of cancer diagnosis." *Id.* at 6-9.

Adami. In October of 2021, using the Danish Prescription Registry, researchers studied 103,565 persons who consumed ranitidine. Hans-Olov Adami et al., *Ranitidine Use and Risk of Upper Gastrointestinal Cancers* 10 (Oct. 7, 2021). Comparing ranitidine users to people who consumed alternative drugs, such as competing H2-blockers or PPIs, the researchers concluded "that our study provides little evidence that ranitidine, whether through NDMA contamination or any other reason, increases risk of upper gastrointestinal cancers." *Id.* at 14. Indeed, for ranitidine users who had obtained 5 or 10 prescriptions of ranitidine, researchers "observed no association" with any cancer. *Id.* at 3.

Nørgaard. The Nørgaard study used the same data set as Adami—the Danish Prescription Registry—and focused on bladder cancer. After identifying 31,393 ranitidine users, the researchers concluded there was "little evidence of any substantially increased risk of bladder" cancer. Mette Nørgaard et al., *Ranitidine and Risk of Bladder and Kidney Cancer: A Population Based Cohort Study* 8, 13 (Oct. 14, 2021). After adjusting for confounding and after using other H2-blockers as active comparators, researchers found "no association" between ranitidine and invasive bladder cancers. *Id.* at 10. This study was published in October of 2021.

Cardwell. Using the Primary Care Clinical Informatics Unit Research database, a general practice database in Scotland, researchers studied a possible link between 455 ranitidine users and bladder cancer. Chris R. Cardwell et al., *Exposure to Ranitidine and Risk of Bladder Cancer: A*

Nested Case-Control Study, Am. J. Gastroenterology, Aug. 2021, at 1, 2, 5. Publishing their results in May of 2021, the authors facially found an association between ranitidine use and bladder cancer when comparing ranitidine users to non-users. *Id.* at 4. The authors also facially found an association with bladder cancer when ranitidine use was compared to the use of PPIs. *Id.* at 5. When comparing ranitidine users to other H2-blocker users, however, researchers found "little evidence of [any] difference in bladder cancer risk." *Id.* at 6. Notwithstanding a facial association between ranitidine and bladder cancer (as compared to non-users of ranitidine and PPI users), the researchers did not conclude ranitidine caused cancer in part because, *inter alia*, "smoking and alcohol [data] were incomplete . . . and consequently, there remains the possibility of residual confounding." *Id.* at 7. In lieu of any conclusion on causation, the researchers recommended further studies "to attempt to replicate [their] findings." *Id.* at 1.

Kim Y. Published in May of 2021, researchers utilized the IBM Explorys database, a private database containing records on over 73 million patients in the United States. Yeseong D. Kim et al., *No Association Between Chronic Use of Ranitidine, Compared with Omeprazole or Famotodine, and Gastrointestinal Malignancies*, 54 Alimentary Pharmacology & Therapeutics 606, 607 (2021) [hereinafter Kim Y et al.]. Identifying 581,028 ranitidine users, researchers compared them to approximately 3 million people who consumed either a competing H2-blocker (famotidine) or PPI drug (omeprazole). *Id.* at 609. As to every cancer the researchers studied (gastric, esophageal, and pancreatic cancer being the ones relevant to this MDL), the researchers concluded that: "[u]se of ranitidine was not associated with an increased odds of developing [cancer]" compared to the other H2-blocker and the PPI studied. *Id.* at 606, 611.

Kantor. Researchers analyzed data on ranitidine users from the Biobank of the United Kingdom, publishing their results in December of 2021. After studying over 459,204 individuals

ranging in age from 38 to 73, where 8,844 reported regular ranitidine use, the study authors concluded: "We found no association between ranitidine use and cancers of the breast, prostate, lung, or colorectum. The exploratory positive association with liver cancer . . . [is] compelling for hypothesis generation, and study findings merit confirmation in other populations." Elizabeth D. Kantor et al., *Ranitidine Use and Cancer Risk: Results from UK Biobank*, 160 Gastroenterology J. 1856, 1856, 1859 (2021). Thus, the researchers found no association for Non-Designated Cancers, but did facially observe an association for liver cancer, a Designated Cancer. *Id.* at 1856, 1858. The researchers did not conclude that ranitidine causes liver cancer, rather they referred to their data on this point to be "compelling for hypothesis generating." *Id.* at 1859. Underscoring this "hypothesis generating finding" and the hesitancy of the researchers to conclude more was the fact that, when ranitidine users were compared to PPI users (those who used omeprazole), the researchers found no association between ranitidine and liver cancer. *Id.* at 1858.

Kumar. Publishing their study in March of 2021, researchers studied gastric cancer using a cohort within the Veterans Health Administration office. Identifying 279,505 patients with long-term prescriptions for acid suppression medications, ranitidine users were compared to other H2-blocker users as well as PPI users. Shria Kumar et al., *Ranitidine Use and Gastric Cancer Among Persons with Helicobacter Pylori*, Digestive Diseases and Scis., Apr. 15, 2021, at 1, 2-3. The conclusion: "There is no demonstrable association between ranitidine use and future gastric cancer." *Id.* at 1. Instead, researchers found that ranitidine users were less likely to develop gastric cancer than those who used other H2-blocker medications, but the researchers "were unable to elucidate the reason behind these findings." *Id.* at 6-7.

McDowell. Published in January of 2021, researchers used the same database as the Cardwell study—the Primary Care Informatics Unit Research database in Scotland. Unlike

Cardwell, however, the McDowell study focused on pancreatic cancer. Researchers found a statistically significant, positive association between ranitidine use and pancreatic cancer when ranitidine users were compared to non-users. R.D. McDowell et al., *The Effect of Medications Associated with Drug-Induced Pancreatic Cancer Risk: A Nested Case-Control Study of Routine Scottish Data*, Cancer Epidemiology, Apr. 2021, at 1, 3-4. Even so, the researchers were not prepared to conclude that ranitidine was associated with pancreatic cancer for at least two reasons. First, there was "no definitive exposure-response relationships" between ranitidine and pancreatic cancer because the adjusted risk rate for those who took the most ranitidine was less (and was not statistically significant) than those who took the least amount of ranitidine. *Id.* at 1, 3. Second, the researchers did not undertake an active comparator analysis between ranitidine users and the users of competing drugs, and the authors noted that another study that did undertake such an analysis actually found a decreased risk of developing pancreatic cancer if one consumed ranitidine. *Id.* at 4. In light of the above, the McDowell authors noted: "[T]he association between ranitidine and pancreatic cancer is yet to be determined." *Id.* at 7.

Yoon. Published in January of 2021, researchers studied ranitidine use via the Health Insurance Review and Assessment Database in South Korea. Studying 11 different cancers and identifying 88,416 ranitidine users, researchers compared the risks of ranitidine use to the use of another H2-blocker (famotidine). Hong Jin Yoon et al., *Risk of Cancer Following the Use of N-nitrosodimethylamine (NDMA) Contaminated Ranitidine Products: A Nationwide Cohort Study in South Korea*, J. Clinical Med., Jan. 5, 2021, at 1, 3. The conclusion: "There was no statistical difference in the overall cancer risk between ranitidine and famotidine," another H2-blocker. *Id.* at 4.

Kim S. Published in August of 2021, this study, like Yoon, was based upon data in South Korea. The Kim S study, however, was based upon the Korean National Health Insurance Service. SunMoon Kim et al., *Effect of Ranitidine Intake on the Risk of Gastric Cancer Development*, Healthcare, Aug. 20, 2021, at 1, 1 [hereinafter Kim S et al.]. The study authors focused on gastric cancer, as compared between ranitidine users and non-users. With this comparison, the computed risk rate for ranitidine was 1.01 with a corresponding confidence interval of .86 to 1.18, and the authors concluded: "Ranitidine intake did not significantly increase the incidence of gastric cancer." *Id.* at 1, 5.

Next, the Court summarizes governmental findings on ranitidine.

The Food and Drug Administration. The FDA found NDMA that exceeded its acceptable daily intake limit in some ranitidine samples. *See supra* Section II(A). The FDA clarified, though, that while it did detect NDMA that eclipsed the regulatory limit in some samples, "[the FDA] didn't observe unacceptable levels of NDMA in many of the samples that [the FDA] tested." Press Release, FDA, FDA Requests Removal of All Ranitidine Products (Zantac) from the Market (Apr. 1, 2021) [hereinafter FDA Apr. 1, 2021, Press Release]. As to the amounts of NDMA found in the samples that were unacceptable, the FDA compared the level found to what "you would expect to be exposed to if you ate common foods like grilled or smoked meats." FDA, *Laboratory Tests | Ranitidine*, https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-tests-ranitidine (last updated Nov. 1, 2019). It called the detected level of NDMA in the samples "low levels" that "would not be expected to lead to an increase in the risk of cancer." FDA Apr. 1, 2021, Press Release, *supra*. Nonetheless, because of the FDA's concern that, in certain situations, the level of NDMA in ranitidine could cross its regulatory limit, the FDA sought a voluntary recall of the drug and continued to run tests on ranitidine. *Id.*

One such test commissioned by the FDA was a randomized, controlled human trial known as the Florian study (referenced above and discussed in Section V(B)(1)(a)(v), *supra*). The purpose of the Florian study was to determine whether ranitidine formed NDMA while inside the human body. *See* Jeffrey Florian et al., *Effect of Oral Ranitidine on Urinary Excretion of N-Nitrosodimethylamine (NDMA): A Randomized Clinical Trial*, 326 JAMA 240, 241 (2021). The FDA scientists conducting the study found that available epidemiological data "d[id] not support that ranitidine is converted to NDMA in a general, healthy population," and that when the authors "consider[ed] all cancer types . . . no consistent signals emerged across studies, and studies with comparison to active controls found no association between ranitidine and overall or specific cancer risk." *Id.* at 241, 247.

The European Medical Association. The EMA analyzed epidemiological data, just as the FDA scientists did. The EMA concluded: "Based on a comprehensive review of epidemiological and post marketing data . . . there is no evidence of a causal association between ranitidine therapy and the development of cancer in patients." EMA, *Assessment Report* 18 (2020).

In summary, it is certainly true that there is no published study or governmental finding that agrees with the Plaintiffs' experts—there is no published conclusion or finding, outside of this litigation, that concludes that ranitidine causes cancer of any kind. Indeed, to the contrary, there is a large amount of evidence for the Defendants' position—evidence that there is no link between ranitidine consumption and cancer. The Plaintiffs' lack of independent scientific support is a valid ground for the Court to grant the Defendants' Epidemiology Motion because it is a valid ground for the Court to question the reliability of the Plaintiffs' experts' methodologies. *See infra* Section VI(A)(4)(a)(iv).

In addition to arguing that there is no widespread acceptance of the Plaintiffs' experts' opinions on general causation, the Defendants also argue that there is no widespread acceptance for the proposition that there is an association—a far lower bar than causation—between ranitidine and cancer. On association the question is a closer one. True, as summarized above, there are a substantial number of studies that conclude that there is not a statistically significant, observable association between ranitidine and cancer. There are a few studies, however, such as Cardwell and McDowell, where the study authors conclude that there is some evidence of an association, although the authors are careful to note the weaknesses in the data showing an association. For example, the Cardwell authors noted a facial association when comparing ranitidine users to non-users but acknowledged that there was no statistically significant association when comparing ranitidine users to users of other H2-blockers. The McDowell authors noted a facial association when comparing ranitidine users to non-users, but they also noted the lack of a dose-response relationship in their data.

Viewing the universe of ranitidine studies in the totality, the Court agrees with the Defendants. Even if there is some evidence of an association in some of the ranitidine studies, there is no widespread acceptance in the scientific community of an observable, statistically significant association between ranitidine and cancer. The Plaintiffs' lack of independent scientific support on association is another valid ground for the Court to grant the Defendants' Epidemiology Motion because it casts further doubt on the reliability of the Plaintiffs' experts' methodology. *See infra* Section VI(A)(4)(a)(iv).

In reaching its conclusion, the Court has confined its analysis on widespread acceptance to studies on ranitidine. As the Court explained in its section framing the general causation question (Section IV, *supra*), the product at issue in this MDL is ranitidine, not NDMA. NDMA is part of

the mechanistic theory by which the Plaintiffs seek to prove that ranitidine can cause cancer. Yet the Plaintiffs focus more on NDMA than they do on ranitidine. By way of example, the Plaintiffs' Response uses the phrases "NDMA in ranitidine" and "NDMA causes cancer" over fifty times. *E.g.,* DE 5915 at 8. The Plaintiffs' characterization of their experts' opinions as NDMA opinions is due in part to their experts' reliance on studies of NDMA in other contexts besides drug ingestion, including the ingestion of NDMA through processed meats and the inhalation of NDMA through rubber factory fumes. *See infra* Section VI(A)(3)(b)(iii). Yet the product in this MDL is neither processed meat nor rubber, and ranitidine is not fungible with or functionally equivalent to NDMA for at least two reasons.

First, the "single most important factor to consider in evaluating whether an alleged exposure causes a specific adverse effect" is "the relationship between the dose and effect." *McClain*, 401 F.3d at 1242. Ranitidine epidemiological studies analyze dose and effect by estimating how much ranitidine someone consumed and then observing whether he or she developed cancer. Studies on NDMA do the same thing—they estimate a dosage of NDMA and see whether cancer develops. *See infra* Section VI(A)(3)(b)(iii). For ranitidine to be "converted" into NDMA, however, some amount of NDMA—a dosage—must be deemed to be the amount of NDMA in ranitidine, and such quantification must be performed through a reliable methodology. As the Court concluded in Section V(A), *supra*, however, the Plaintiffs' expert on quantifying the amount of NDMA in ranitidine (Dr. Najafi) has been stricken as unreliable.

Second, the Plaintiffs do not allege that ranitidine contains any harmful agent other than NDMA. In contrast, NDMA studies on food ingestion and fume inhalation involve many other carcinogens besides NDMA. The potential confounding effects of many other carcinogens

necessitates its own explanation from an expert, so that the Court may ensure that the expert has utilized a reliable methodology to account for confounding.

It is for at least these two reasons that ranitidine is not simply *interchangeable* with NDMA—any conversion from ranitidine to NDMA is more complicated than that. Stated differently, while an apple may simply be compared to another apple, for an apple to be compared to an orange the comparison must be accompanied with an explanation. In this MDL, a more apt comparison would be that of an apple—dietary studies—with medicine—ranitidine. This comparison certainly requires a scientific explanation. And the explanation must be a part of a reliable methodology, consistent with *Daubert*.

At this point in the Court's analysis, the Court need not address whether the Plaintiffs' experts' usage of non-ranitidine studies is part of a reliable methodology or not—that is a subject the Court addresses in Section VI(A)(3)(b)(iii), *infra*. What the Court can say, however, is that for the reasons outlined above and in Section VI(A)(3)(b), *infra*, the Court is persuaded by the Defendants' argument that there is no widespread acceptance amongst independent scientists of the Plaintiffs' experts' opinions; there is no widespread acceptance that **ranitidine** causes cancer.

Similarly, as will be discussed in more detail below, there is no widespread acceptance of the Plaintiffs' experts' weight-of-the-evidence and Bradford Hill methodologies, which weigh dietary studies and occupational studies equal to or more strongly than ranitidine studies, and which weigh comparisons between ranitidine users and non-users more strongly than comparisons between ranitidine users and the users of similar medications. Because the Court's conclusions on widespread acceptance are at least partially founded on the reliability of comparisons of ranitidine users to non-users and because such comparisons raise important issues in this MDL, the Court will now address at length the role of comparators in the Plaintiffs' experts' methodologies.

b. **Reliability of Plaintiffs' Experts' Analysis of Available Data**

The Defendants contend that the Plaintiffs' experts' analyses and methodologies are unreliable for several reasons: (i) the experts do not properly account for potential bias and confounding in ranitidine epidemiology, (ii) the experts ignore sound statistical principles in ranitidine epidemiology, and (iii) the experts rely upon irrelevant, non-ranitidine epidemiology for their opinions. Each point is addressed in turn.

i. Plaintiffs' Experts' Accounting for Bias and Confounding in Ranitidine Epidemiology

The Defendants argue that the Plaintiffs' experts' opinions are unreliable because their opinions do not properly control for confounding variables. For their part, the Plaintiffs argue that their experts did properly account for confounding variables.

As for the underlying need to control for confounding, confounding is a form of bias, and an epidemiologist "must account for the roles of bias [and] confounding factors." *Magistrini*, 180 F. Supp. at 604. This principle does not mean that a study may only be relied upon by an expert if it fully and completely addresses all potential sources of confounding, but it does mean that confounding is a source of bias that must be considered in a causation opinion. As to this point, the Plaintiffs' experts agree. *E.g.,* McTiernan Report at 41 ("For both case-control and cohort studies, the populations should be well-characterized, so that any potential confounding variables can be accounted for. . . .").

In the Court's summary of epidemiological concepts above in Section VI(A)(1), the Court used the example of age as a potential confounding variable. Age is a confounding variable in the Court's example because it was independently related to both hair color and risk of death. In this MDL, smoking may be a confounding variable because it can independently relate to both

ranitidine use (ranitidine users may smoke more than the general population)[86] and to some types of cancer. If ranitidine users smoke more than non-users of ranitidine (such as the general population), ranitidine users would be more likely (all else being equal) to develop cancer than non-users. One possible way to control for the potential confounding effect of smoking is through the use of active comparators.

To explain active comparators, suppose the prevalence of smoking for ranitidine users is generally the same as the prevalence of smoking for those who use other H2-blockers. Provided that this is the case and the smoking rates of ranitidine users and other H2-blockers are the same or similar, if the cancer risk of ranitidine use is compared to the cancer risk from using other H2-blockers (an active comparison), the potential of smoking risk to confound the results is at least partially reduced because both groups under scrutiny are equally likely to develop cancer from smoking.

Almost all of the ranitidine epidemiological studies in this MDL used active comparisons with H2-blockers and PPIs to analyze the impact of confounding factors. The prevalence of this active comparator analysis is explained, by way of example, in the following excerpt from Nørgaard: "[W]e lacked information on smoking, which is an important risk factor for bladder cancer, and other lifestyle choices such as [body mass index]. However, smoking and other lifestyle factors are unlikely to be strongly related to [the] choice of type of H2-blocker thus the active comparator-design likely averted potential confounding by these." Nørgaard et al., *supra*, at 13. If the researchers in Nørgaard had complete and accurate information on smoking prevalence rates—for ranitidine users and for non-users—the researchers could have eliminated (through complicated math) the potential confounding effect of smoking on the study results. But

[86] *E.g.,* McTiernan Report at 145 ("[A]lcohol and smoking are related to risk for both [sic] pancreatic, bladder, and stomach cancers, and could be related to propensity to use ranitidine.").

they "lacked [that] information," and therefore could not mathematically excise the confounding effect of smoking from their results. *Id.* Instead, the Nørgaard researchers attempted to indirectly adjust for smoking confounding through another method—through the use of an active comparator, the users of other H2-blockers. Because "smoking and other lifestyle factors are unlikely to be strongly related to [the] choice of" ranitidine or some other H2-blocker, the researchers compared the cancer rates of these two groups of people in their effort to account for smoking confounding. *Id.*

Even though almost every ranitidine epidemiological study, including Nørgaard, utilized an active comparator analysis, and even though such a method, if properly designed, helps eliminate bias through confounding, the Plaintiffs' experts contend that all ranitidine epidemiology findings based upon active comparators should be disregarded.[87] *E.g.,* Moorman Report at 152 (describing reliance on active comparator data as "impossible"). Yet many study authors thought that active comparators were proper and useful, putting the study authors at odds with the Plaintiffs' experts.

The Defendants argue that the Plaintiffs' experts' disregard for the active comparisons in ranitidine epidemiology is unreasonable and renders the Plaintiffs' experts' methodologies unreliable; in short, the Defendants argue that the Plaintiffs' experts have no valid, science-based reason to completely disregard all active comparisons. Below, the Court summarizes the results of the active comparator analyses in the 10 epidemiological studies on ranitidine, as well as how those analyses impacted the researchers' ultimate conclusions.

[87] The Plaintiffs' experts have other criticisms of ranitidine epidemiology besides the issue of active comparators. For examples of Dr. McTiernan's and Dr. Moorman's criticisms specific to active comparators and ranitidine, see the Court's discussion in Section VI(A)(4)(c), *infra*.

Iwagami. In their analysis of gastric cancer risk, researchers specifically designed their study as an active comparator study to eliminate bias through confounding; they compared ranitidine users to users of other H2-blockers. The researchers conducted an active comparator analysis, at least in part, to account for confounding by indication, which they saw as a primary confounding factor. Iwagami et al., *supra*, at 3. Confounding by indication occurs, according to the Iwagami authors, when the very symptoms that cause one to need an acid suppression medication are simultaneously symptoms of developing cancer, such as peptic ulcers.[88] *See id.* Thus, by comparing two groups of acid suppression medication users, the authors sought to eliminate confounding by indication.

Distilled down, the researchers' ultimate conclusion was a computed ranitidine risk rate of 1.01, with a corresponding confidence interval of .95 to 1.08. *Id.* at 6. Because this confidence interval contained a range below 1 and above 1, the researchers did not consider the computed risk of 1.01 to be statistically significant.[89] Thus, citing their active comparator analyses, the researchers concluded "there is no significant association between ranitidine[] and the incidence of cancer diagnosis." *Id.* at 9.

Adami. Like Iwagami, the Adami study authors designed their study to compare ranitidine users to the users of other H2-blockers. Also like Iwagami, the Adami authors utilized an active comparator analysis to account for confounding by indication. Adami et al., *supra*, at 6. The Adami study compared ranitidine users to an additional group of users that Iwagami did not utilize, those who used PPI acid suppression medication (a stronger medication than H2-blockers).

[88] The Plaintiffs' experts concede as much: "Ranitidine, other H2 blockers, and protein pump inhibitors (PPIs) are used for the treatment of many gastro-intestinal disorders, such as ulcers, esophagitis, heartburn, gastro-esophageal reflux disorder (GERD), and other, rarer, conditions. The symptoms for many of these (such as stomach pain, heartburn, nausea) are common early symptoms of stomach cancer." McTiernan Report at 258.
[89] The Court addresses the concept of statistical significance in detail, below, in Section VI(A)(4)(b)(ii).

Studying gastric cancer and actively comparing ranitidine users to other H2-blockers, researchers computed a risk rate of .98 with a corresponding confidence interval of .84 to 1.14. *Id.* at 4. For esophageal cancer, the risk rate was 1.09 with a confidence interval of .91 to 1.29. *Id.* Finally, for pancreatic cancer, the risk rate was .97 with a confidence interval of .87 to 1.10. *Id.* Noting that all of the active-comparator driven risk computations lacked statistical significance, the authors concluded that there was "no compelling evidence" that ranitidine increases cancer risk and that there was "no [observable] association" when the researchers confined their analysis to subjects who consumed the highest amount of ranitidine (those who obtained 10 or more ranitidine prescriptions). *Id.* at 1.

Nørgaard. Studying bladder cancer, researchers utilized an active comparator analysis to account for confounding by indication and to account for a lack of data on smoking rates for the subjects under study. Nørgaard et al., *supra*, at 12, 13. Using an H2-blocker comparison, researchers computed a risk rate of 1.11 with a confidence interval of .95 to 1.29. *Id.* fig. S2. Noting this statistically insignificant risk rate, researchers concluded that there was "little evidence of any substantially increased risk of bladder" cancer and that there was "no association" between ranitidine and invasive bladder cancers. *Id.* at 10, 13.

Cardwell. Studying bladder cancer, Cardwell also compared ranitidine users to H2-blocker users and PPI users to account for confounding by indication. Cardwell et al., *supra*, at 4. Cardwell is one of only two ranitidine studies in this MDL to report a statistically significant positive association for cancer risk when ranitidine users are compared to PPI users, computing a risk rate of 1.20 with a confidence interval of 1.04 to 1.39.[90] *Id.* at 5. When the Cardwell researchers compared ranitidine use to the use of other H2-blockers, however, the study results

[90] The other study to find a statistically significant risk rate as compared to PPI users was Nørgaard.

showed no statistically significant association with a risk rate of 1.05, accompanied by a confidence interval of .86 to 1.28. *Id.* The Cardwell authors conclusion was merely that "further studies [were] necessary to attempt to replicate" their findings. *Id.* at 7.

Kim Y. Researchers studied gastric, esophageal, and pancreatic cancer. Comparing ranitidine users to the users of other H2-blockers, researchers found that ranitidine showed a lower risk rate of .51, with an accompanying confidence interval of .43 to .6.[91] Kim Y et al., *supra*, at tbl.3. As compared to PPI users, the risk of ranitidine consumption was .62, with an accompanying confidence interval of .52 to .72. *Id.*

Kantor. For liver cancer, the study authors compared ranitidine users to both non-users and PPI users. The Kantor study did not include a comparison between ranitidine use and the use of other H2-blockers. When ranitidine users were compared to non-users, the study authors found a statistically significant risk rate of 1.91, with a confidence interval of 1.09 to 3.36. Kantor et al., *supra*, at 1856. When ranitidine use was compared to PPI use, however, researchers computed a statistically insignificant confidence interval of .58 to 2.26, with a risk rate of 1.15. *Id.* In light of this data and the smaller number of cases, the Kantor authors described their findings as "an exploratory positive association" for "hypothesis generation" that "merit[s] confirmation in other populations." *Id.* at 1859.

Kumar. For gastric cancer, the Kumar study compared ranitidine users to other H2-blocker users and to PPI users. Those who used competing H2-blockers were found to be more likely than ranitidine users to develop cancer (1.83 calculated risk, with a confidence interval of 1.36 to

[91] The numbers for each type of cancer were similar. The Court sets forth here only the number associated with patients taking ranitidine in comparison to patients taking famotidine, omeprazole, and rates of esophageal cancer.

2.48).[92] Kumar et al., *supra*, at 4. As compared to PPI users, however, researchers found no discernable difference in risk (.92 calculated rick, with a confidence interval of .82 to 1.04). *Id.*

McDowell. Studying pancreatic cancer, the McDowell study is one of only two ranitidine studies that did not utilize an active comparator analysis; McDowell only compared ranitidine use to non-use. Compared to non-use, the ranitidine adjusted risk rate was a statistically significant 1.37 with a corresponding confidence interval of 1.1 to 1.7. McDowell et al., *supra*, at 3. However, this computation came with conflicting internal data because, if ranitidine were to cause cancer, one would expect greater exposure to ranitidine to result in greater incidences of cancer (a dose-response relationship). The study authors found that when a ranitidine user took a larger dosage—six or more prescriptions of ranitidine—the risk rate was both lower and statistically insignificant: 1.24 with a corresponding confidence interval of .91 to 1.69. But when ranitidine users took a smaller dose—five or fewer prescriptions of ranitidine—the risk rate was higher and statistically significant: 1.49 with a corresponding confidence interval of 1.12 to 1.99. Based upon this inconsistency, the researchers concluded: "[N]o definitive exposure-response relationship[] between [ranitidine] and cancer risk [was] observed," "the association between ranitidine and pancreatic cancer is yet to be determined," and "further studies of the association between ranitidine and pancreatic cancer" should take place. *Id.* at 7.

Yoon. Yoon, like most of the studies described above, compared ranitidine use to the use of other H2-blockers. The Yoon study included more cancers than any other study, reviewing 11 cancers. Yoon et al., *supra*, at 1. The study authors found no statistically significant association

[92] The risk rate in Kumar is presented differently than the risk rates in all other studies because the risk rate is for the comparison of H2-blockers to ranitidine, not ranitidine to other H2-blockers. Were the risk rate to be recomputed to a risk rate comparison of ranitidine use to the use of other H2-blockers, the risk rate for ranitidine would be less than one.

for any cancer, and the overall cancer risk was a statistically insignificant .99 with a corresponding confidence interval of .91 to 1.07. *Id.* at 4.

Kim S. The Kim S study was the second of two studies that focused on comparisons to non-users. Using that comparison, the study authors computed a statistically insignificant risk rate for ranitidine of 1.01, with a corresponding confidence interval of .86 to 1.18. Kim S et al., *supra*, at 5.

Across all of the ranitidine epidemiological studies,[93] four uniform trends emerge. First, no study found a statistically significant positive association between ranitidine and cancer when ranitidine use was compared to the use of other H2-blocker medications. Second, with two exceptions (Cardwell and Nørgaard), every study to compare ranitidine use to the use of PPI medications found no statistically significant positive association between ranitidine and cancer. Third, with two exceptions (McDowell and Kim S), every study utilized an active comparator analysis to address potential confounding in the study's results. Fourth, comparing ranitidine users to non-users generally resulted in a higher computed risk of cancer than comparing ranitidine users to the users of another acid suppression drug.

In summary, the results of the ranitidine studies' active-comparator analyses, together with the study authors' conclusions on the analyses, are uniformly unhelpful for the Plaintiffs. Therefore, if the Plaintiffs' experts disregard active comparator study designs without a scientific basis for doing so, it would suggest that the experts' disregard for active comparator data was an outcome-driven decision, not a science-based decision. And it could also suggest that the experts' criticisms of ranitidine epidemiology on other grounds (besides the active comparator study design) are not the true reasons that the experts assigned no or little weight to the studies.

[93] The Court addresses a new study, the Wang study, below in Section VI(A)(4)(c).

What then are the Plaintiffs' experts' opinions on the active comparator study designs? The Plaintiffs' experts agree, at least in the abstract, that active comparators are a useful tool to eliminate confounding. By way of example, Dr. Moorman considers active comparator study designs to be a "typical approach" to address confounding by indication. Moorman Report at 24-25. Confounding by indication arises in the ranitidine epidemiology, the Defendants assert, supported by their own expert testimony,[94] because ranitidine users are more likely than the general population to have conditions that predispose them to certain types of cancer such as ulcers or Barrett's esophagus. The Plaintiffs' experts agree that those who seek ranitidine prescriptions may do so because of symptoms that are caused by a developing cancer. For example, in her expert report on page 145, Dr. McTiernan states that "alcohol and smoking are related to risk for both [sic] pancreatic, bladder, and stomach cancers, and could be related to propensity to use ranitidine." She also states that GERD is treated with acid suppressants and "may be [an] early symptom[] of esophageal cancer." *Id.* at 206. As for Dr. McTiernan's testimony on the subject:

> Q. But you do know that patients with diabetes may have symptoms that would lead them to take acid suppressants; correct?
>
> A. It could.
>
> . . . .
>
> Q. So smoking, obesity, and alcohol are risk factors for cancer incidence, correct?
>
> A. For different types of cancer, yes.
>
> . . . .
>
> Q. Do you know or do you not know that patients with Barrett's esophagus are commonly treated with acid suppressant medications?
>
> A. It's my understanding that patients with Barrett's—diagnosed Barrett's esophagus, that a treatment plan for them would include acid suppressants.

[94] *E.g.,* Terry Report at 25; Witte Report at 6. The Court cites to the Defendants' experts' reports for completeness, but the Court's decision is not based upon the content of the Defendants' experts' reports.

. . . .

> Q. Okay, Doctor, you note in your report, and I think we just read this, that medical conditions, such as H.pylori, hep B and C infection, diabetes, Barrett's esophagus, are all risk factors for cancers of the stomach, liver, pancreas and esophagus, respectively, correct?
>
> A. That's what I wrote, yes.

. . . .

> Q. H. pylori, diabetes, Barrett's esophagus, these are all risk factors for cancer incidence, correct?
>
> A. For some types of cancer, yes.

. . . .

> Q. And these conditions could cause symptoms leading patients to take ranitidine or comparator drugs; right?
>
> A. Yes.

McTiernan Dep. at 160, 163-65, 169-70.[95] From Dr. Moorman's deposition:

> Q. Okay. So at least for these three cancers, the underlying conditions of the ranitidine patients at baseline could confound an analysis that compares ranitidine users to non-users; is that right?
>
> A. One with [sic] certainly want to consider the underlying condition being treated when interpreting the results from the study, yes.
>
> Q. And why did you single out gastric, esophageal, and possibly liver cancer here?
>
> A. The literature does indicate that some of the risk factors for these cancers include conditions that could be treated with acid-suppressing drugs. So for example, esophageal cancer, GERD or gastric esophageal reflux disease is considered a risk factor for gastric cancer. Ulcers, H. pylori infection could be considered risk factors. And then for liver cancer, although cirrhosis is not an approved or listed on the indications for either H2 blockers or for PPIs, there is some literature that suggests that they are prescribed for patients with cirrhosis.

[95] The closest the Plaintiffs' experts come to refuting the proposition that the same symptoms that can cause cancer can also generate a need for acid suppressants is through the occasional assertion of ignorance on the subject. *E.g.,* McTiernan Dep. at 156 ("Q. So leaving aside the issue of confounding in study design, do you or do you not know whether the patient population in the United States that uses acid suppressants is more likely to smoke than the general population that doesn't use acid suppressants, do you know? A. I don't know if I've seen a paper that says that, that looks in the general population of ranitidine users or H2-blocker users compared to non-users.").

> Q. And in at least these three examples, why would it be difficult to sort out whether any increased risk of cancer observed with use of acid-suppressing use of drugs is due to the drug itself or the condition being treated that was responsible for the increase in risk? . . . .
>
> A. Again, there are—there is the potential that it is the underlying condition, and there is also the potential that the drug itself could contribute to the increased risk. And there are ways to approach that, including looking at the risk for different conditions and seeing how—you know, attempting to sort out the risk from the drug itself from the underlying condition.

Moorman Dep. at 175-77.[96]

It is a very intuitive, common-sense proposition that those who suffer from chronic symptoms that generate the need for many years[97] of acid suppressant consumption are, at least on average, less healthy than a population of people who do *not* need to consume acid suppressants for many years—a non-user population. It is therefore unsurprising to this Court that eight ranitidine study authors chose to compare ranitidine users—who suffer from certain confounding symptoms that generate the need for ranitidine—with those who suffer from similar symptoms but consume a competing acid suppressant drug. To contest the decision by the eight study authors to compare ranitidine to competing medications to help control for confounding, the Plaintiffs' experts offer two critiques.

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[96] The prevalence of the confounding factors discussed above is visible in the ranitidine epidemiologic data as well. For example, in Kantor, ranitidine users were more likely to have a higher BMI than non-users, and they were more likely to smoke as well. Kantor et al., *supra*, at supplementary tbl.1. In Cardwell, ranitidine users were more likely than non-users to have ulcers, Barrett's esophagus, diabetes, and tobacco use. Cardwell et al., *supra*, at tbl.1. The prevalence of confounding factors in ranitidine users also is visible in this MDL. At the time of this Order, there remain approximately 50,000 ranitidine users (out of an original 150,000) that have either filed a complaint in this MDL or recorded their intent to file a complaint in a registry of claims. According to census forms completed by the claimants, over 23,000 of those ranitidine users either smoke or have type 2 diabetes. The Plaintiffs have relied upon Registry information in their Response to the Epidemiology Motion. DE 5915 at 62.

[97] *See* DE 5915 at 18 (representing that 60% of the Plaintiffs have consumed ranitidine for more than 10 years).

The Plaintiffs' Experts' First Critique of an Active Comparator Study Design

First, the Plaintiffs' experts contend that the characteristics of ranitidine users and the characteristics of the users of other H2-blockers[98] are *not* similar, rendering a comparison between these two populations unworthy of credence. *See* McTiernan Dep. at 686. This criticism misdirects from the truly germane question, which is not whether differences may be found in the population of ranitidine users and the population of users of competing drugs, but is instead whether the population of those who use competing drugs is *more similar* to ranitidine users than those who do not use acid suppressants at all (i.e., non-users).

As for the Plaintiffs' experts' specific criticism, Dr. Moorman admits that the FDA-approved indications for other H2-blockers are similar to the indications for ranitidine. Moorman Dep. at 193. The same is true of Dr. McTiernan. At her deposition, Dr. McTiernan was unable to name any label indications for ranitidine that differ from label indications for another H2-blocker. McTiernan Dep. at 135.

As for the germane question, whether the population of non-users is more similar to ranitidine users than the population of those who use competing drugs, Dr. Moorman's report states that there "may" be differences in prescription choices between users, Moorman Report at 28-29, but she later admitted that she was unable to "find a lot of published data" reporting "characteristics of [] other H2-blockers as compared to ranitidine" or any data demonstrating that ranitidine users are more similar to non-users than they are to the users of other H2-blockers,

[98] The Court's focus is on H2-blockers because most of the studies and most of the parties' arguments focus on this question. The Court believes that there is no real dispute between the parties that alternative H2-blockers function similarly to ranitidine, which is itself an H2-blocker, and are therefore more similar to ranitidine than PPI drugs, which function differently. Thus, while PPI users would be more similar to ranitidine users than the general population, and the Plaintiffs' experts provide no basis to dispute this position, the Court can see no reasonable basis to conclude that PPIs make for a better ranitidine comparator than H2-blockers. *E.g.,* Moorman Report at 211 ("PPIs have been shown to be more effective in suppressing acid than H2RAs . . . . Because of their greater effectiveness, patients treated with PPIs are likely to have a more serious underlying condition or more severe symptoms.").

Moorman Dep. at 193-94, 345-47. And Dr. McTiernan, at her deposition, was unable to name a single study that shows that ranitidine users are more similar to non-users than to the users of other H2-blockers. McTiernan Dep. at 717-19. Additionally, Dr. McTiernan's report states that "[f]amotidine [an H2-blocker] and ranitidine have similar clinical efficacy, and therefore it is not clear why one is chosen over the other by prescribing physicians." McTiernan Report at 134.

The Court need not quantify or weigh how similar ranitidine users are to the users of other H2-blocker medications. What matters is whether the users of other H2-blockers make for a more reliable comparison than people who do not use acid suppressants at all.[99] On this issue, the Plaintiffs' experts have provided no reliable justification for their criticism of active comparators. The Plaintiffs' experts' lack of justification stands in contrast to the opinions of every published researcher to have considered the subject. *See, e.g.,* Iwagami et al., *supra*, at 9 ("[S]uch a comparison is less prone to indication bias than a comparison between users and non-users of ranitidine/nizatidine.").

The Court does not mean to suggest or conclude that an active comparator analysis is automatically reliable or is the only avenue for a reliable methodology. That too is not the issue. The issue is whether, based upon the facts and studies in this MDL, a reliable methodology may disregard active comparator analyses *in a specific study* in favor of comparisons to non-users *in the very same study*, something that both Dr. McTiernan and Dr. Moorman do in their expert reports. On this question, the Plaintiffs' experts' first critique amounts to speculation, and it runs counter to every published study to have considered the subject.

[99] The Court does not mean to suggest that an active comparator analysis is necessarily more reliable than a comparison of users to non-users where confounding is controlled for through other means. A number of studies compared ranitidine users to non-users and attempted to control for confounding based upon available data. The Court's point is that the Plaintiffs' experts have provided no justification for the idea that all ranitidine active comparator analyses should be disregarded because non-users are more similar to ranitidine users than the users of similar medications.

The Plaintiffs' Second Critique of an Active Comparator Study Design

Second, the Plaintiffs' experts take a position of enormous consequence to the public health—that every H2-blocker and every PPI, all of them, cause cancer. Because every H2-blocker and every PPI causes cancer, the Plaintiffs contend, H2-blockers and PPIs cannot be used as valid comparators for ranitidine. But, upon questioning, the Plaintiffs' experts decline to defend an opinion on this matter.

Dr. McTiernan's discussion on the subject:

> Q. Okay, okay. So in your report, Dr. McTiernan, you claim that PPIs are an inappropriate comparator in the studies of ranitidine and cancer risk because they purportedly increase the risk of cancer; correct?
>
> A. Can you point to where you're—what you're mentioning?
>
> Q. Well, let me rephrase. Do you, Dr. McTiernan, believe that PPIs increase the risk of cancer?
>
> A. I referenced a few papers that did show that, increased risk of some cancers in PPI users.
>
> Q. I understand that you reference some papers. My question to you is, Dr. McTiernan, do PPIs increase the risk of cancer?
>
> A. I referenced a couple of papers that showed an association. I did not do a systematic review and a causal analysis of PPIs and cancer.
>
> Q. Okay. So do you have an opinion as to which cancers PPIs are associated with?
>
> A. I would need to look at which papers I've referenced, but since I didn't do a systematic review of PPIs and cancer, I couldn't say which cancers are associated and which are not.
>
> Q. Okay. So as you sit here today, you can't tell me—you can't name a single cancer that PPI use is associated with?
>
> A. I did not do a systematic review.
>
> . . . .
>
> Q. Okay, Dr. McTiernan, so you didn't do a systematic review of PPIs and cancer risk. Did you do a systematic review for any other H2-blocker and cancer risk?

A. My systematic review was focused on ranitidine. But in order to search, I also searched on H2-blockers.

Q. Is it your opinion that any H2-blocker other than ranitidine increases cancer risk?

A. No, it's not my opinion.

McTiernan Dep. at 171-75. Dr. Moorman on the subject:

Q. Is it your opinion, Dr. Moorman, within a reasonable degree of scientific certainty, that H2RAs other than ranitidine cause any of the five cancers in this lawsuit? . . . .

A. I did not do a full causal analysis of other H2RAs and these cancers. I indicated as here that there is evidence to support that.

Q. Why didn't you do a full causal analysis similar to what you've described on pages 5 to 6 of your report?

A. My focus was on ranitidine exposure. I certainly looked at many of the papers related to PPIs and H2RAs, but I did not go through the full detailed analysis that I did for ranitidine.

Q. So is it fair to say that you do not hold an opinion within a reasonable degree of scientific certainty that other H2RAs cause any of the five cancers in this lawsuit?

A. Once again, I indicated that I reviewed a lot of those papers, but I did not go through the full Bradford Hill analysis as I did with ranitidine and these cancers.

Q. In your opinion, Dr. Moorman, is it well established and generally accepted in the scientific community that these other H2RAs increase the risk of or cause any of the five cancers? . . . .

A. Once again, I did not do the full detailed causal analysis as I did with ranitidine.

Q. To the best of your knowledge, has the FDA, IARC, the American Cancer Society, or any other institution concluded that the other H2RAs cause or increase the risk of any of the five cancers?

A. I am not aware if they have done a complete review and causal assessment in that regard.

Q. To the best of your knowledge, do the FDA-approved labels for any of the other H2RAs warn that those drugs increase the risk of any of the five cancers?

A. I know that I cited the package inserts for some of the drugs in my report. I don't recall—I mean, certainly, we can pull them up, but I don't recall if there was any mention of that in the package labeling.

Q. Have you told anyone outside this litigation your view that H2RAs increased the risk of gastric cancer, liver cancer, and pancreatic cancer?

A. I am rereading the question. I have not had a discussion with anyone outside of the litigation on this topic.

Q. Do you think it's widely understood within the relevant treatment communities that these other H2RAs increase the risk for certain types of cancer? . . . .

A. I cannot speak to what is understood in the treatment community. I can speak to the—some of the published literature that I cited that does indicate increased risk for these cancers among users of these drugs.

Q. Well, throughout your report, you use the phrase "general acceptance" or "generally accepted" or "well established." Can you say that it's generally accepted with—in the relevant cancer treatment communities that these other H2RAs increase the risk of any of the five cancers? . . . .

A. Okay. You know, again, based on the studies that I cited, there certainly is published literature to support my position. And as I said, I cannot speak to what is held widely—held generally accepted.

Q. And I believe you told me a couple of minutes ago that you did not do a complete search of the public literature on this topic; is that right?

A. I don't—I am trying to—I certainly looked at this literature, and again, I did not evaluate it with—to the same degree that I did the ranitidine and cancer risk. But I've certainly considered the literature.

Q. Some of the literature.

A. I— . . . . As I said, I looked at many of the studies. I think that it was a thorough representation of what is in the literature.

Q. If these other H2RAs are causing cancer, that would be a pretty significant public health problem, wouldn't it, Dr. Moorman?

A. These are drugs that are widely used, and it would be—you know, for that reason, if they are causing cancer, yes, it would be an important public health problem.

Moorman Dep. at 179-84.[100]

Neither Dr. Moorman nor Dr. McTiernan provides support for the proposition that any researcher or governmental body has **concluded** that every (or any) H2-blocker and PPI causes cancer, nor have they provided any support for the proposition that it is generally known that such drugs cause cancer. And since the Plaintiffs' experts disavow that they have, in this litigation, a specific expert **opinion** that those drugs cause cancer, they have provided no scientific explanation or methodology to support such an opinion that this Court could evaluate for reliability. Additionally, by failing to offer an opinion, the Plaintiffs' experts fail to offer any explanation why all other H2-blockers and PPIs cause cancer through a non-NDMA mechanism—such as altering a stomach's acid balance—but how that very same (**unpled**) mechanism is not the causal culprit in this MDL.

The Plaintiffs' experts therefore speculate via unoffered opinions. And the Court cannot imagine this MDL if these unoffered opinions about other H2-blockers and PPIs causing cancer were admissible and presented to a jury because it would be tantamount to a never-ending mini-trial on the question of whether other H2-blockers and PPIs cause cancer, all in the context of experts who disavow opinions of the same.

The Plaintiffs' experts' criticisms of active comparators run counter to the conclusions put forward in every published ranitidine epidemiological study. Therefore, it falls upon the Plaintiffs' experts to provide a reliable reason why an active comparator analysis within a study may not be credited, but a non-user analysis within the very same study may. *E.g., Norris*, 397 F.3d at 882 ("We are simply holding that where there is a large body of contrary epidemiological evidence, it is necessary to at least address it with evidence that is based on medically reliable and scientifically

[100] Neither Dr. McTiernan nor Dr. Moorman cite to the Krawczynski or Matsuda studies discussed in Section V(B)(2), *supra*.

valid methodology."). The Plaintiffs' experts failed to defend any such reason at their depositions. Juxtaposed to the Plaintiffs' experts' criticisms of active comparators is the fact that, *after* the Plaintiffs' experts completed their expert reports and they were deposed, the Plaintiffs' experts' criticisms ceased. Their criticisms ceased when the first ranitidine study with statistically significant active comparator data was published. *See infra* Section VI(A)(4)(c) (discussing this issue at length). Soon after that publication, the Plaintiffs' experts pivoted to concluding that a comparison of ranitidine to a similar drug is an analytical strength; in doing so, the Plaintiffs' experts no longer took the position that, because every H2-blocker and every PPI causes cancer, those drugs should not be compared to ranitidine.

In summary, the Court agrees with the Defendants that the Plaintiffs' experts have failed to justify their criticisms of ranitidine active comparator analyses. Because of this, combined with the fact that the active comparator data (together with study authors' conclusions on that data) more strongly favors the Defendants' position, not the Plaintiffs', the Court agrees with the Defendants that the Plaintiffs' experts' disregard of active comparator data is indicative of outcome-driven reasoning and is, therefore, indicative of an unreliable methodology. More specifically, the Plaintiffs' experts' uniform decision to credit comparisons with healthier, non-users of ranitidine (which better favors their opinions) *in conjunction* with the exclusion of comparisons with similar medications in the very same studies (which less favors their opinions) is evidence of an unreliable, outcome-driven methodology.[101]

Additionally, the Court agrees with the Defendants that an analysis that credits comparisons with non-users in a study, but disregards comparisons to similar medications in the very same study does not reliably account for confounding bias. Finally, the Court agrees with the

[101] The Defendants have labeled this "selective science," and the Court addresses this topic in greater detail in Section VI(A)(4)(c), *infra*.

Defendants that the Plaintiffs' experts' decision to disregard active comparator study designs while relying upon non-comparator data from the very same studies casts doubt on the Plaintiffs' experts' critiques of active comparator studies on other grounds. The Court will address the ramifications of these conclusions in Section VI(A)(4), *infra*, in the context of specific expert's opinions.

Although the Court has referenced the statistical significance of various studies' findings above, the Court has thus far not addressed the issue of statistical significance in any real depth. The Court does so now.

ii. Statistical Significance and Ranitidine Epidemiology

As summarized by the Court in Section VI(A)(1)(c), *supra*, the statistical significance of a study's results is tied to the study's confidence interval. The confidence interval in turn is a determination of how much randomness and chance could have influenced a study's results. If study authors can conclude with 95% confidence that an association is positive and is not negative, then the results are considered statistically significant. Conversely, if study authors can conclude with 95% confidence that an association is negative and is not positive, that too would be a statistically significant finding. In the example below taken from the Defendants' Epidemiology Motion, Exhibit C, the Adami study results are not statistically significant while the Kim Y results are statistically significant.

If study authors allow for greater uncertainty and greater random chance, they could reduce their level of certainty from 95% to 90% or some other, lower number. In doing so, the confidence interval would narrow and include a smaller range of numbers both to the left (the lower end of the range) and to the right (the higher end of the range). Conversely, study authors could increase

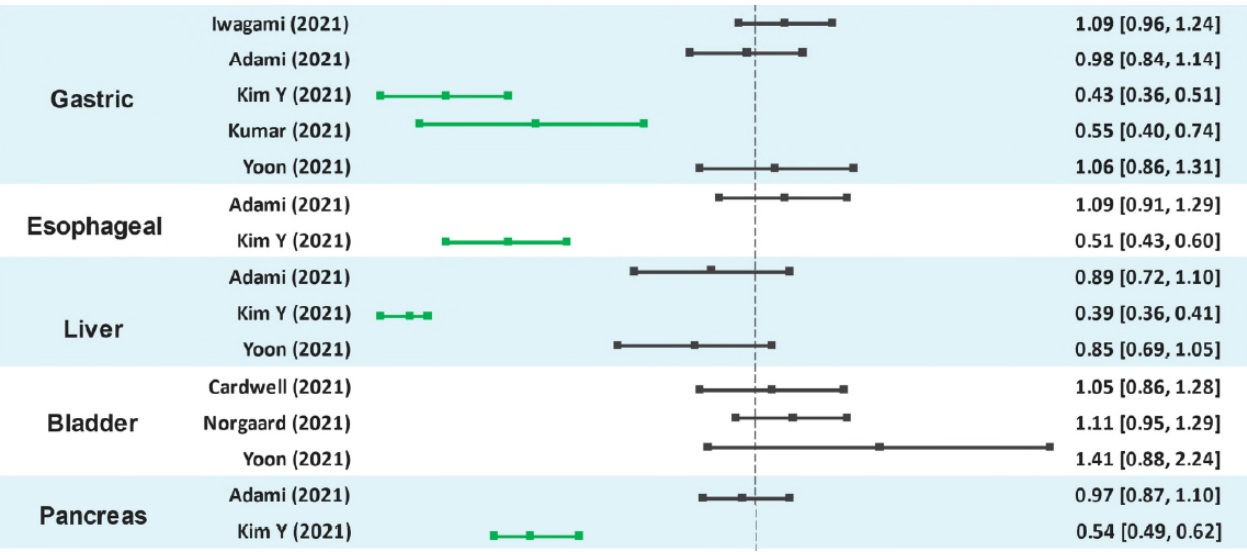
the level of certainty in their results and adjust their confidence interval from 95% to 99%. In doing so, the confidence interval would widen and include a larger range of numbers.

The 95% confidence threshold has become, according to the Reference Manual on Scientific Evidence, an "icon[] of science and legal process." *Reference Manual on Scientific Evidence*, *supra*, at 252.[102] Pursuant to the Reference Manual, case law, and the Plaintiffs' experts' own admission, it is standard practice for confidence intervals to be computed using a 95% threshold and, should results "cross the 1," the results are not statistically significant and are, all else being equal, entitled to lesser weight and lesser reliance.

The 95% confidence interval threshold for statistical significance is not a mandatory practice, with the Reference Manual calling the 95% confidence interval "at best [a] useful convention." *Id.* Stated another way, if a study's results are statistically insignificant, that facial lack of significance is not dispositive on the question of admissibility. The Supreme Court has stated as much: "A lack of statistically significant data does not mean that medical experts have no reliable basis for inferring a causal link between a drug and adverse events . . . . [M]edical experts rely on other evidence to establish an inference of causation." *Matrixx Initiatives, Inc. v. Siracusano*, 563 U.S. 27, 40 (2011). District Courts routinely hold the same: "'[S]tatistical significance, by itself, should not mechanically control whether an epidemiological analysis is sufficiently reliable to be admissible.' But as many federal courts observe, 'if an expert places undue emphasis on statistically insignificant evidence, it may indicate that the expert's methods are unreliable.'" *In re Prempro Prods. Liab. Litig.*, 738 F. Supp. 2d 887, 892 (E.D. Ark. 2010).

[102] The Plaintiffs, as well as the Court, have utilized and relied upon the Reference Manual. *E.g.,* DE 5915 at 55.

Below, the Court includes the results from seven ranitidine epidemiological studies (taken from an appendix to the Epidemiology Motion) that compared ranitidine use to the use of other H2-blockers, none of which found a statistically significant positive association:



To summarize, then, seven ranitidine epidemiological studies that compared ranitidine users to the users of H2-blockers found no statistically significant association between ranitidine and a Designated Cancer: Iwagami, Adami, Yoon, Kim Y, Kumar, Cardwell, and Nørgaard. An eighth study, the Kantor study, found no statistically significant association between ranitidine and the only comparator drug tested, a PPI. A ninth study, the Kim S study, found no association between ranitidine and non-users of ranitidine.

The Defendants argue that the Plaintiffs' experts place too much emphasis on statistically insignificant findings, rendering their opinions unreliable, while the Plaintiffs contend that their experts' opinions on statistical significance are consistent with routine scientific practice. The Court addresses specific experts' reliance on statistically insignificant data in Section VI(A)(4), *infra*. What the Court can say as a general matter, however, is that in light of the above-referenced statistically insignificant results from active-comparator based ranitidine epidemiology, it is

unsurprising that the Plaintiffs' experts rely in great part upon epidemiology that did not study ranitidine, and it is to this evidence that the Court now turns.

iii. Plaintiffs' Reliance on Non-ranitidine Epidemiology

Instead of relying solely upon ranitidine epidemiology, the Plaintiffs' experts rely in great part upon dietary epidemiology, studies focused on NDMA-rich foods that cancer victims consumed before a cancer diagnosis, and an occupational study[103] that examined the cancer risks stemming from rubber production in the United Kingdom. The Defendants argue such reliance equates to an unreliable methodology, while the Plaintiffs argue that the reliance was necessary and appropriate. The Court addresses the Plaintiffs' dietary studies first and then addresses the Plaintiffs' study on rubber production.

Dietary Studies

The Court summarizes the dietary studies that the Plaintiffs' experts rely upon below. The Court divides the studies into two categories. First, prospective dietary studies where participants described their diets before they developed cancer. Second, retrospective dietary studies where participants described their diets after they developed cancer.

Prospective Dietary Epidemiology

With one exception, none of the prospective dietary studies cited by the Plaintiffs' experts found a statistically significant positive association between NDMA-rich foods and a Designated Cancer. After summarizing the prospective studies below, the Court discusses three overarching weaknesses in all of the dietary epidemiology, at least as they are applied to this MDL. The first such weakness is the potentially confounding effect of carcinogens in the large-scale consumption of NDMA-rich foods (processed meats). Another is the uncertain amount of NDMA at issue in

[103] The Plaintiffs' experts do cite and discuss additional occupational studies; however, the Court does not discuss those studies for the reasons set forth in this section.

this MDL and the Plaintiffs' evidentiary burden regarding the same. And the third is an apparent discrepancy in risk assessments arising from dietary epidemiology when the Plaintiffs' experts apply dietary epidemiology to the facts of this MDL.

Loh. The Plaintiffs' experts rely upon a study from the United Kingdom, which Dr. McTiernan calls "key," that estimated the risks of NDMA consumption for a variety of different cancers, including esophageal and stomach cancer. McTiernan Report at 170; Yet Hua Loh et al., *N-nitroso Compounds and Cancer Incidence: The European Prospective Investigation into Cancer and Nutrition (EPIC)—Norfolk Study*, 93 Am. J. Clinical Nutrition 1053, 1053 (2011). The study authors selected 23,363 people that did not have cancer, and each completed a questionnaire about the types of food that they ate. *Id.* at 1054. The questionnaire asked participants what food they had eaten in the prior twenty-four hours and what food they had eaten in the preceding week. *Id.* The questionnaire also contained a list of foods and beverages and asked the participants to rate the frequency with which they consumed the foods and beverages in the preceding year. *See id.* Based upon these questionnaires, the study authors estimated how much NDMA each participant consumed on a given day. *Id.*

This estimation resulted in a bottom quartile of consumption of 16.8 ng per day and top quartile of consumption at 125.9 ng per day. *Id.* at 1057. Following the participants for 11 years and identifying 3,268 cancer victims, the bottom three quartiles of NDMA consumption (for all cancers studied) did not show a statistically significant positive association with cancer. *Id.* When the authors compared NDMA consumption to specific cancers, however, the authors computed a risk rate (for 47 ng of NDMA[104] per day) of 1.13 for esophageal cancer and 1.13 for stomach cancer. *Id.* at 1059. These estimates were not statistically significant, however, as the

[104] The Court has relied upon Dr. McTiernan's representation that these figures are based upon NDMA consumption of 47ng per day. McTiernan Report at 168.

corresponding confidence intervals were .77 to 1.68 and .81 to 1.57. *Id.* For the two Designated Cancers at issue in this MDL, the authors concluded: "There was no significant association with esophageal and stomach cancers." *Id.* at 1056-57.

Jakszyn. The Plaintiffs' experts rely upon a 2011 study, Jakszyn, that focused on 481,419 participants in 10 European countries. Paula Jakszyn et al., *Red Meat, Dietary Nitrosamines, and Heme Iron and Risk of Bladder Cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC)*, 20 Am. Ass'n for Cancer Rsch. 555, 555 (2011). Using similar food questionnaires as Loh and following participants for a mean of 8.7 years, the study authors divided estimated NDMA daily intake into roughly the following four quartiles: 0 ng, 50 ng, 100 ng, and 190 ng. *Id.* at 556 tbl.1. For bladder cancer, the authors computed risk rates of 1.14, 1.07, and 1.12 for the second, third, and fourth quartiles. *Id.* None of these risk rates were statistically significant, however, as the associated confidence intervals were .91 to 1.42, .85 to 1.34, and .88 to 1.44. *Id.* The study authors described these findings as a "lack of association" and "we found no overall association between intake of red meat (fresh and processed meat), nitrosamines, or heme iron and bladder cancer risk." *Id.* at 558.

Knekt. Dr. McTiernan relies[105] upon a Finnish study of 9,985 individuals, where study authors compared NDMA consumption to stomach cancer[106] using the now-familiar food questionnaire model. Paul Knekt et al., *Risk of Colorectal and Other Gastro-Intestinal Cancers After Exposure to Nitrate, Nitrite and N-nitroso Compounds: A Follow-Up Study*, 80 Int'l J. Cancer 852, 852 (1999). The mean NDMA intake was estimated at approximately 52 ng. *Id.* Comparing the highest quartile of NDMA consumption to the lowest quartile, the study authors found a

[105] Dr. Moorman includes this study in a table of epidemiological studies that she analyzed and cites to the study a few times; Dr. Moorman assigned "little" weight to the study.
[106] This study also examined the risks associated with Non-Designated Cancers.

decreased risk of stomach cancer of .75. *Id.* at 853. Thus, this study showed evidence of a reverse dose-response relationship, with more NDMA consumption resulting in less relative risk. *Id.* The authors' ultimate conclusion was: "[W]e found no notable association between intake of NDMA and incidence of stomach cancer." *Id.* at 855.

Larsson. Dr. McTiernan relies[107] upon a study of dietary habits of Swedish women from 2006. That study was based upon dietary questionnaires that were sent in the mail to prospective participants. Susanna C. Larrson et al., *Processed Meat Consumption, Dietary Nitrosamines and Stomach Cancer Risk in a Cohort of Swedish Women*, 119 Int'l J. Cancer 915, 915 (2006). A total of 61,433 women completed the questionnaires and were enrolled in the study. *Id.*

Daily NDMA intake was divided into quintiles. *Id.* at 918. The first, second, third, and fourth quintiles did not exhibit a statistically significant positive association for gastric cancer. *Id.* The final quintile was comprised of 31 participants who consumed greater than 194 ng of NDMA per day. *Id.* Comparing the fifth quintile to the first quintile, the study authors found evidence of a statistically significant positive association: 1.96 with a confidence interval of 1.08 to 3.58. *Id.* Important for the Court's analysis below, the study authors concluded that the foregoing was evidence of an association between the excess consumption of *processed meat* and stomach cancer, because the highest source of NDMA in the participants' diet was processed meat. *Id.* The authors found that processed meat could account for as much as 80% of NDMA dietary intake. *Id.* Ultimately, the study authors concluded that the NDMA in processed meats "might" account for the positive association seen in the data. *Id.*

Keszei. The Plaintiffs' experts rely upon a study of 120,852 people in the Netherlands who completed food questionnaires. As with all other dietary studies, NDMA intake was estimated

[107] Although Dr. Moorman cites to this study throughout her report, it is not clear to the Court how much this study impacted Dr. Moorman's analysis.

based upon the answers in the questionnaires, with the median NDMA consumed per day computed to be roughly 84 ng. András P. Keszei et al., *Dietary N-Nitroso Compounds, Endogenous Nitrosation, and the Risk of Esophageal and Gastric Cancer Subtypes in the Netherlands Cohort Study*, 97 Am. Clinical Nutrition 135, 136, 139 (2013). Of significant importance to the analysis of this Court, *infra*, almost all of the NDMA consumption of the highest-NDMA-consuming participants came from processed meats and beer. *Id.* at 138.

For women, no statistically significant association for esophageal or stomach cancers was observed. *Id.* at 141. For men, no statistically significant association for either cancer was observed for the bottom two tertiles of NDMA consumption. *Id.* For men in the third tertile, based upon 29 participants who developed it, the study authors found a statistically significant risk of 2.43, with a confidence interval of 1.13 to 5.23, for one subtype of esophageal cancer. *Id.* Also for men in the third tertile, depending on how the study authors adjusted for confounding and based upon 125 participants who developed it, the study authors found a statistically significant risk of 1.41, with a confidence interval of 1.05 to 1.90, for one subtype of stomach cancer. *Id.* The study authors concluded that they had found evidence of a positive association between NDMA-intake and cancer. *Id.* at 145.

Processed Meat. The first weakness of the dietary epidemiology is the potentially confounding effect of carcinogens in the large-scale consumption of NDMA-rich foods. A recurring theme in all of the dietary studies in this MDL is that when NDMA consumption is high, most of the NDMA comes from processed meat, salted meat, barbequed meat, or in some instances, beer.[108] It is therefore worth observing, even if it is somewhat obvious, that no study participant's NDMA consumption was high because the participant consumed pure NDMA on its

[108] Beer/alcohol is a known potential confounding variable for cancers in this MDL. McTiernan Dep. at 155-56.

own. Accordingly, it is somewhat inaccurate to refer to these dietary studies, as the Plaintiffs do in their court filings, as "NDMA studies" or "NDMA epidemiology," because what the studies truly examine is the association between *foods* that *contain* NDMA and cancer. This distinction is important because foods contain far more than just NDMA. Foods can contain non-NDMA carcinogens which, of course, can cause cancer independently of NDMA.

IARC classifies processed meats as a "Type I Carcinogen." McTiernan Dep. at 506. This classification stems in part from the fact that processed meats contain nitrosamines. *Id.* at 507-09. NDMA is one nitrosamine, but there are hundreds of known nitrosamines. *See id.* And while not every nitrosamine can be found in processed meats, other carcinogenic nitrosamines found in processed meats include NDEA, NPIP, and NYPR. *C.f. id.* at 510 ("I know there are several. I don't have the names of them off the top of my head."). Grilled, processed, and smoked meats also contain toxic compounds such as polycyclic aromatic hydrocarbons, heterocyclic aromatic amines, and acrylamide, which Dr. McTiernan concedes. *Id.* at 510-11. The Plaintiffs' experts also concede that processed meats contain other potential cancer risks such as high levels of fat, salt, and iron. Moorman Report at 52. Stated in simpler terms, many of the harmful agents in processed meats, aside from the NDMA, could have caused a person's cancer. This is likely why, in studies such as Larsson, the study authors concluded that there was a positive association between processed meat consumption and cancer, and, while NDMA "might" be the cause of that association, the researchers were left uncertain whether NDMA was, in fact, the cause. Larsson et al., *supra*, at 915.

<u>NDMA in this MDL</u>. Another weakness of the dietary epidemiology is the uncertain amount of NDMA at issue in this MDL. As the Court discussed at length in Section V, *supra*, the amount of NDMA exposure from ranitidine is a controversial subject in this MDL. Consistent

with the Court's prior rulings, the expert that the Plaintiffs retained to estimate the amount of NDMA in ranitidine (Dr. Najafi) utilized an unreliable, inadmissible methodology. Therefore, the Plaintiffs' evidence, viewed in the light most favorable to the Plaintiffs, approximates the average amount of NDMA in ranitidine at 144 ng per 150 mg pill, as seen in an average of the FDA and the Defendants' tests. *See supra* Section V(A), (C); Salmon Report at 212. As a result, dietary epidemiology that studied the risk of cancer arising from much higher amounts of NDMA is not a good fit for this MDL. Additionally, for a participant in a dietary study to consume 144 ng of NDMA on a daily basis, the participant's consumption of processed meats would be great indeed which, as discussed above, would be accompanied with an equally large consumption of non-NDMA carcinogens and related confounding factors.

Risk Assessment of NDMA. A third weakness of the dietary epidemiology is an apparent discrepancy between the FDA's risk assessment of NDMA and the Plaintiffs' experts' risk assessment of NDMA which, unlike the FDA, is based upon dietary epidemiology. As noted above, the average amount of NDMA found in ranitidine by the FDA and the Defendants was slightly above the FDA's acceptable daily limit of 96 ng per 150 mg pill. According to the FDA's own risk assessment, consuming 96 ng every day for 70 years would result in 1 in 100,000 people developing cancer, or a .001% chance that a consumer developed cancer as a result of the NDMA consumption. *See infra* Section VII(B).[109] This FDA risk assessment, assuming it is correct, is consistent with the ranitidine epidemiology that found no statistically significant association between ranitidine and cancer, but the FDA's risk assessment stands in stark contrast to the Plaintiffs' experts' risk assessment. For example, using dietary epidemiology as the basis for his calculations, Dr. Salmon computes a 57% increased risk of esophageal cancer from 1.81 years of

[109] Of course, ranitidine has only been sold for 39 or so years, not 70.

ranitidine consumption.[110] Salmon Report at 221, 223. The FDA's risk assessment and the Plaintiffs' experts' risk assessment therefore differ by many orders of magnitude.

The facial discrepancy between the varying risk estimations could be explained in the Plaintiffs' favor by the fact that the (lower) FDA risk assessment is ultimately derived from animal studies (which require extrapolation to humans), while the (higher) dietary-based risk assessments are based upon humans and, thus, require no species extrapolation. Alternatively, the facial discrepancy could be explained in the Defendants' favor by the fact that the (lower) FDA risk assessment is limited to the risk of NDMA consumption alone (animals were injected with NDMA), while the (higher) dietary-based risk assessments are premised upon much more—the risk from the combination of every component of a person's diet, together with accompanying lifestyle, and not just NDMA.[111] Either way, the Court need not address the large disparity between the FDA's risk assessment and the Plaintiffs' dietary-based epidemiology risk assessments because the Plaintiffs' experts are ultimately excluded from testifying for many other, independent reasons.

Retrospective Dietary Epidemiology[112]

Turning back to the dietary studies relied upon by the Plaintiffs' experts, the Court summarizes the retrospective dietary studies wherein patients who were diagnosed with cancer were asked to describe their historical lifetime eating habits. First, the Court addresses a type of inherent unreliability in these sorts of studies: the accuracy of exposure.

[110] If Dr. Salmon's risk assessment is correct, the Court would presume that ranitidine epidemiology would quickly detect a statistically significant association between ranitidine use and cancer. The Court would not intuit, as the Plaintiffs argue, that 14 years of observation would be an insufficient amount of time to detect an increased risk from ranitidine use.

[111] Additionally, the Plaintiffs' experts' risk assessment is based upon Dr. Najafi's laboratory tests, which this Court found to be unreliable in Section V(A), *supra*.

[112] Dr. McTiernan relies upon a few studies not discussed in this Order: Palli, La Vecchia, Gonzalez, Risch, and Chyou. The Court deems discussion of these studies to be unnecessary; the Court's discussion of the other dietary studies adequately sets forth the basis for the Court's rulings.

The Accuracy of Exposure. A general difficulty inherent in the usage of dietary studies to estimate cancer risk is the fact that when such studies are conducted retrospectively, the subject of interest has already developed cancer. Cancer victims can struggle to remember what their diets were over the course of their lifetime and thus accurately estimate the volume of the unhealthy foods that they ate. The Plaintiffs' expert, Dr. McTiernan, expounded on this general difficulty with dietary studies when she testified as an expert in a different litigation:

> Once somebody develops cancer, their diet changes dramatically. If you want to know what somebody's previous diet effect of cancer risk is, it is very difficult to do that in a case-control study. The person has already changed. Diet, you can't ask somebody what they have eaten in the past.

McTiernan Dep. Ex. 28 at 7; *In re Talc* Jan. 25, 2019, Daubert Hearing at 737-38. In the course of that same litigation, Dr. McTiernan testified:

> The amount that people eat, what they're eating, how often they're eating, the variables are so difficult to collect, that the results from case-control studies are a concern to some investigators.

Brown Decl., DE 5692 Ex. 33; *In re Talc* Jan 28, 2019, Dep. at 115. In this litigation, Dr. McTiernan testified that she could not recall her earlier testimony on this topic, but she nonetheless agreed that "[it] can be difficult in case-control studies to make sure that there isn't recall bias for diet studies, **that is why [the World Cancer Research Fund] has historically not used—or not relied as much on case-control studies**." McTiernan Dep. at 496-97 (emphasis added).

Here, in this MDL, the Plaintiffs' experts argue that the accuracy of exposure is not an issue because patients tend to underestimate—not overestimate—the unhealthy foods they ate and, as a result, there is a bias towards the null and a finding of no association, not a bias of too much association. *E.g.,* McTiernan Report at 170 ("Diet was assessed at only one timepoint in these studies which reduces accuracy of diet variables and biases the relative risk toward the null value."); *see also* Moorman Report at 49. The Plaintiffs' experts repeatedly contradict their

position on accuracy of exposure, however, because they base their opinions on the comparative relative risk from the highest quartile of daily NDMA consumption to the lowest quartile of daily NDMA consumption. Moorman Report at 10 ("[W]hen the data are in categories rather than binary, [exposure] misclassification does not always result in a bias towards the null."); McTiernan Dep. at 211-27. There is no bias towards the null when one compares the highest quartile of NDMA consumption to the lowest quartile of NDMA consumption because the comparison is between one potentially inaccurate quartile to another potentially inaccurate quartile. This potential for inaccuracy becomes even more pronounced when the sample sizes are relatively small which, as will be seen, is characteristic of the retrospective dietary epidemiology in this MDL.

Zheng. The Plaintiffs' experts rely upon a hospital-based case-control study of 827 patients who were diagnosed with liver cancer. J. Zheng et al., *Dietary N-nitroso Compounds and Risk of Hepatocellular Carcinoma: A USA-Based Study*, 74 J. Hepatology 3161, 3161 (2021). Diagnosed patients were given food questionnaires that were used to estimate NDMA consumption. *Id.* at 1. The study found that overall NDMA consumption was not positively associated with cancer risk, with a risk rate of .80. *Id.* When NDMA consumption was limited to animal-based foods, the risk rate increased but was not statistically significant: 1.26 with a confidence interval of .83 to 1.91. *Id.* When NDMA consumption was limited to plant-based foods, the risk rate became statistically significant, albeit barely: 1.54 with a confidence interval of 1.01 to 2.34. *Id.* Faced with somewhat conflicting data between meat consumption and plant consumption, the study authors speculated that the participants lowered their intake of meat before their diagnosis, signifying an inherent problem with the study design's accuracy of exposure. *See id.* The study authors concluded: "NDMA . . . effects . . . warrant further prospective investigation." *Id.*

De Stefani. Dr. McTiernan relies[113] upon a study of 340 stomach cancer patients in rural Uruguay. Eduardo De Stefani et al., *Dietary Nitrosamines, Heterocyclic Amines, and Risk of Gastric Cancer: A Case-Control Study in Uruguay*, 30 Nutrition & Cancer 158, 158 (1998). The patients completed dietary questionnaires after their diagnoses. *Id.* at 159. Compared to the NDMA consumption of other dietary studies in this MDL, the daily intake of NDMA in De Stefani was high. The lowest quartile of daily NDMA intake was 140 ng and the highest was 270 ng. *Id.* at 161 tbl.4.

This high NDMA intake is a result of the participants' unusually high consumption of salted and barbequed meat. *Id.* at 158. As much as 80% of the population of Uruguay consumes a large amount of barbequed meat. *Id.* Barbequed meat contains potent carcinogens. *Id.* Because of the dietary habits in rural Uruguay, the study authors specifically chose to study gastric cancer risks in that population. *Id.* Thus, somewhat unsurprisingly the study participants' high consumption of meat with carcinogens resulted in statistically significant risk rates for stomach cancer throughout the quartile ranges, from 2.07 to 3.62. *Id.* at 161. The study authors' conclusion was: "[T]his case-control study suggests that red meat intake and chemicals resulting from its cooking are associated with a significant increase in the risk of gastric cancer in the Uruguayan population." *Id.*

Ronco. Dr. Moorman relies upon another Uruguayan study. That study focused on 225 subjects who were diagnosed with bladder cancer. Alvaro Luis Ronco et al., *Meat Consumption, Animal Products, and the Risk of Bladder Cancer: A Case-Control Study in Uruguayan Men*, 15 Asian Pac. J. Cancer Prevention 5805, 5805 (2014). Just like De Stefani, the subjects consumed very large quantities of NDMA through meat. *See id.* Also like De Stefani, the subjects with high

[113] Dr. Moorman includes this study in her table of analyzed studies, however, she does not cite to the study in her report.

NDMA intake,[114] as compared to those with much lower NDMA intake, showed statistically significant risks of cancer as high as 2.14. *Id.* at 5807. The study authors concluded as follows: "In conclusion, the present study showed that total meat, processed meat, hot dog, ham, salted meat, boiled eggs, fried eggs, total eggs, and whole milk were positively associated with increased risk of bladder cancer." *Id.* at 5808.

Rogers. The Plaintiffs' experts rely upon a study out of Washington state. Study participants were 125 persons who were newly diagnosed with esophageal cancer. Mary A. M. Rogers, *Consumption of Nitrate, Nitrite, and Nitrosodimethylamine and the Risk of Upper Aerodigestive Tract Cancer*, 4 Cancer Epidemiology Biomarkers & Prevention 29, 29 (1995). After their diagnosis, the participants were asked to complete a food questionnaire, and researchers estimated NDMA intake from the food questionnaire. *Id.* The study did not find a statistically significant positive association between NDMA consumption and esophageal cancer, even at the highest intake of NDMA per day (greater than 179 ng per day); they found a relative risk of 1.86 with a corresponding confidence interval of .87 to 3.95. The study authors therefore reported no observable relationship between NDMA and esophageal cancer.[115] *See id.* at 34.

Pobel. The Plaintiffs' experts rely upon a study of 92 patients in France who were diagnosed with stomach cancer. Dominique Pobel et al., *Nitrosamine, Nitrate and Nitrite in Relation to Gastric Cancer: A Case-Control Study in Marseille, France*, 11 Eur. J. Epidemiology 67, 67 (1995). After a cancer diagnosis, the 92 patients completed food questionnaires. *Id.* at 68. The estimated daily intake of NDMA in Pobel was very high, ranging from 200 ng in the bottom quartile to 510 ng in the highest quartile. *Id.* at 69. Comparing the highest quartile of NDMA intake to the third quartile resulted in a statistically significant positive association of 7.00 with a

[114] The Court is unable to discern the estimated levels of NDMA intake from the study or from Dr. Moorman's report.
[115] The researchers did report an observable association for certain Non-Designated Cancers.

confidence interval of 1.85 to 26.46. *Id.* at 67. The study authors concluded that, "assuming current diet adequately reflects past diet" (which the Court addressed above under "accuracy of exposure"), "NDMA could be a marker of overall intake of foods . . . and may therefore contribute to different stages of the carcinogenic process." *Id.* at 70-71.

Song. The Plaintiffs' experts rely upon a meta-analysis of eleven dietary studies that looked at stomach cancer; the eleven studies included several of the studies listed above such as Knekt and Jakszyn. Peng Song et al., *Dietary Nitrates, Nitrites, and Nitrosamines Intake and the Risk of Gastric Cancer: A Meta-Analysis*, 7 Nutrients 9872, 9874-76 (2015). After pooling data from the eleven studies, the authors computed a comparative cancer risk rate for those who consumed the highest amount of NDMA compared to those who consumed the least amount of NDMA, finding the rate to be 1.34 with a corresponding confidence interval of 1.02 to 1.76. *Id.* at 9885. The authors of the study were not prepared to conclude that NDMA dietary intake is associated with stomach cancer, noting the inherent uncertainties of dietary questionnaires and other confounding factors, and instead concluded that "[m]ore well-designed large prospective studies are needed to help us understand these substances in the etiology of gastric cancer." *Id.* at 9893.

The Plaintiffs' Occupational Study on Rubber Workers

In addition to dietary epidemiology, the Plaintiffs' experts rely upon an occupational cohort study (Hidajat) of 36,441 men who worked in a rubber factory in the United Kingdom.[116] Mira Hidajat et al., *Lifetime Exposure to Rubber Dusts, Fumes and N-nitrosamines and Cancer*

[116] The Plaintiffs' experts briefly discuss two other rubber factory NDMA studies, Vlaanderen and Straif, but both studies' results were statistically insignificant; both studies had a small number of cases; both studies had minimal data quantifying exposure; both studies receive minimal discussion in the experts' reports; and Dr. Moorman assigns "little weight" to the results of Vlaanderen. Moorman Report at 105, 201; McTiernan Report at 190. The Court therefore does not believe that Vlaanderen or Straif warrant any additional discussion or analysis—the Court's analysis on Hidajat controls.

Mortality in a Cohort of British Rubber Workers with 49 Years Follow-Up, Occupational & Env't Med., Feb. 16, 2019, at 250, 250. Rubber creation leads to the formation of many different types of carcinogens, with the carcinogens being so prolific in the workplace that IARC has classified occupation in the rubber industry as a "Group 1" (known) carcinogen. DE 5699 at 93. One of the carcinogens generated in rubber creation is NDMA, and NDMA was a primary focus of the Hidajat study. Hidajat et al., *supra*, at 250. The study collected data on where the men worked in the rubber factory in the year 1967. *Id.* The goal of the study was to measure any association between the workers' NDMA exposure and cancer. *Id.*

Data on the workers' NDMA exposure in 1967 did not exist. *See id.* at 251. Based upon employment records that showed the department where each worker worked, however, the study authors estimated each worker's level of NDMA exposure based upon the location and duties of the worker's department. *Id.* Data on workers' employment (and therefore exposure to NDMA) before 1967 was not available. *Id.* Similarly, data on workers' employment after 1967 was not available. *Id.* The study authors therefore assumed that each worker stayed in the same department until they reached 70 years of age. *Id.* At that age, the study authors assumed the workers retired. *Id.* Based upon these assumptions, the study authors estimated the level of NDMA each worker received through inhalation of fumes and dust in the air via their occupation. *Id.* Because the year of focus, 1967, was so far in the past, the study authors were able to conduct 49 years of follow-up to see which workers developed cancer. *Id.* Whether any worker had, after 1967, been exposed to a non-NDMA carcinogen or otherwise had some predilection for cancer was unknown to the researchers. *Id.*

Combining all of the above-referenced assumptions and estimations, the study authors compared the relative risk of the factory workers who were estimated to have inhaled the greatest

amount of NDMA to that of the factory workers estimated to have inhaled the least amount of NDMA. *See id.* at 251-52. The authors found statistically significant risk rates of many different cancers, including all of the Designated Cancers in this MDL, for high NDMA exposure. *Id.* at 252. Dr. McTiernan's report indicates that this study "contributed highly" to her causation opinions. McTiernan Report at 164. Dr. Moorman's report indicates that she assigned "moderate weight" to the study. Moorman Report at 105.

Conclusion

The Court concludes that an expert opinion that relies upon the dietary or occupational studies discussed above to conclude that ranitidine can cause cancer utilizes an unreliable methodology for the three reasons highlighted in **bold** below. Furthermore, the Court concludes that any such methodology would be unreliable for three additional reasons. However, those additional reasons apply not just to dietary and occupational studies, but also more broadly to ranitidine studies, and the Court therefore addresses those additional grounds for exclusion in Section VI(A)(4)(a)(iv), *infra*.[117] For now, the Court confines its discussion to conclusions that are specific to dietary and occupational studies.

First, there are too many inherent uncertainties in the dietary epidemiology and the Plaintiffs' occupational study for such data to be reliably applied to the causation question in this MDL. Specific to dietary epidemiology, as quoted above, Dr. McTiernan has conceded case control dietary epidemiology is subject to inaccuracies and misclassification, and Dr. Moorman concedes this point in her expert report as well. *E.g.,* Moorman Report at 129 (noting the "challenges of assessing diet in epidemiological studies"). The Plaintiffs' experts further concede

[117] The three additional grounds for exclusion are that the Plaintiffs' experts lack widespread scientific acceptance for their conclusions, widespread acceptance for their methodologies, and that Dr. McTiernan places undue reliance upon statistically insignificant data.

that the "components of processed meats could contribute to cancer risk, including salt and fat content, heme iron and other carcinogens" which further attenuates the results of dietary epidemiology (which is really, for all intents and purposes, epidemiology on high levels of meat consumption) from the general causation question in this MDL. Moorman Report at 52. Indeed, IARC has classified processed meat as a "known" carcinogen while NDMA is classified as a "probable" carcinogen.

The Plaintiffs' experts' methodology, then, is to use data from food questionnaires (a first analytical leap assuming the accuracy of a subject's memory), which was used to estimate lifetime food consumption (a second analytical assuming never-changing eating habits), which was used in turn to estimate NDMA consumption (a third analytical leap assuming average NDMA values in food), even though other carcinogens were present in the food (a fourth analytical leap that attempts to account for other carcinogens), to estimate a cancer risk (a fifth analytical leap controlling for other confounders, such as smoking), even though much—and perhaps even the vast majority—of the data was statistically insignificant (a sixth analytical leap over random chance). Then, the Plaintiffs use the data to answer a causation question about medicine (a seventh analytical leap comparing diet to medicine). The Plaintiffs' experts leap too far. Trial courts are "free to 'conclude that there is simply too great an analytical gap between the data and the opinion proffered,'" and the gap here is too great. *Hendrix II*, 609 F.3d at 1194 (quoting *Joiner*, 522 U.S. 136 at 146).

Specific to the Hidajat occupational study, the number of assumptions and estimations necessary to render this study helpful to a jury are staggering. Hidajat's assumptions included that: workers continued to work in the factory after 1967; workers retired at age 70; workers never ceased to work until they were 70; workers never moved to another department with different

NDMA-exposure levels; and workers never left the rubber industry to be exposed to different carcinogens in some other occupation. Additionally, an estimation was necessary to compute the amount of NDMA each worker breathed in his department, given that such data was never recorded. Finally, the study authors had to try to adjust for confounding variables and for the possibility that other carcinogens in the rubber factory could have caused a worker's cancer. Given these assumptions, estimations, potential for confounding, and calculations, Dr. McTiernan concedes that "the dose and length of exposure may not have been accurately ascertained *if at all*." McTiernan Report at 58 (emphasis added).

Dr. Hidajat, a primary author of the study, filed a rebuttal expert report in this MDL wherein she defends the assumptions she made and the design of her study; perhaps, consistent with her rebuttal report, her assumptions and study design served her purposes well. But her study's purpose was not to answer the question at issue in this MDL. The Hidajat study conclusion reads as follows:

> In summary, we examined the exposure-response association **between occupational exposures to rubber dust, rubber fumes and nitrosamines** with cancer mortality . . . . Consistent with previous studies, N-nitrosamines exposures **in the rubber industry**, were associated with mortality from cancers . . . . Furthermore, **exposures to rubber dust and rubber fumes** were found to be associated with higher risks for these cancers as well. Results from this study contribute to the evidence of elevated cancer mortality risks **from occupational exposures in the rubber industry** by further clarifying the relationship between each carcinogen and cancer with implications **for the industry today** where occupational exposures to N-nitrosamines continues to persist, although at greatly reduced levels compared with several decades ago.

Hidajat et al., *supra*, at 257-58 (emphasis added). The study was focused on the rubber industry; it was focused on the inhalation and skin absorption of toxic vapors from rubber creation.

Dr. Hidajat admits that her study was not designed to assess NDMA exposure through an oral medication. Hidajat Dep. at 53-55, 144-46. The route of exposure—skin absorption,

inhalation, and ingestion—is no small matter. "[T]hose routes affect the magnitude of ultimate exposures and because they often affect health outcomes" in different ways. *Reference Manual on Scientific Evidence*, *supra*, at 518. Dr. Hidajat admits that she is not qualified to draw any conclusions about whether inhalation or skin absorption of NDMA is analogous to NDMA exposure via oral medication, and neither Dr. McTiernan nor Dr. Moorman even attempt to offer such an opinion. Hidajat Dep. at 53-55, 144-46. When an expert relies on the studies of others, she "must not exceed the limitations the authors themselves place on the study. That is, [s]he must not draw overreaching conclusions." *In re Accutane Prods. Liab.*, 511 F. Supp. 2d at 1291 (citing *McClain*, 401 F.3d 1233 at 1245-47). The Plaintiffs' experts' reliance on Hidajat "exceeds" the boundaries of what that study set out to prove, and the Plaintiffs' experts' reliance on the study amounts to an "overreaching conclusion."

For the Hidajat study to possess some level of relevance, an expert would have to testify at trial[118] that the inhaled and absorbed fumes from a 1967 rubber factory may be reliably converted into an ingested dose of ranitidine. The Court believes such a conclusion would also "exceed the limitations the authors themselves place on the study," as the Hidajat study was clearly meant to address the risks of exposure from an occupation, rubber creation. And of course, for such a conversion to be part of a reliable methodology, it would also have to be weighed in conjunction with assumptions about how long a worker worked, where they worked, and what they were exposed to. Then further assumptions and estimations would be necessary for comparison, such as how much NDMA is in ranitidine, how long a Plaintiff consumed ranitidine, and historical levels of NDMA in ranitidine, among other factors.

[118] The Plaintiffs have designated Dr. Andrew Salmon as the expert who would offer this opinion.

At some point, there can "simply [be] too great an analytical gap between the data and the opinion proffered" for the *Daubert* standard to be satisfied. *Joiner*, 522 U.S. at 146. Here, with assumption piled upon assumption, estimation piled upon estimation, and with route-of-exposure conversions being necessary for the data in Hidajat to be applied to this case, the analytical leap from the Hidajat data to the operative inquiry in this MDL is simply too great. The Court deems any methodology that relies upon 1967 rubber factory worker toxic fume inhalation to conclude that an unspecified amount of ranitidine ingestion (discussed in the subsequent paragraph) causes cancer is an unreliable methodology.

Second, the analytical gap discussed by the Court above means that the dietary and occupational studies have only attenuated relevance to the question at hand. Those studies did not focus on ranitidine, they focused on NDMA. Yet the Plaintiffs' experts rely heavily[119] on the studies. *See infra* Sections VI(A)(4)(a)(iv), (b)(iii). The Plaintiffs argue that because ranitidine can contain NDMA, their experts' heavy reliance was justified, but this is an unpersuasive argument under analogous Eleventh Circuit case law.

In *Chapman*, the product at issue was Fixodent denture adhesive. 766 F.3d at 1300. The *Chapman* plaintiff argued that excessive zinc in Fixodent caused her neurological damage. *Id.* Although the scientific community did not recognize the toxicity of or potential for Fixodent to cause neurological damage, the plaintiff argued that the scientific community did, as a general matter, recognize the toxic potential of zinc. *Id.* at 1304. Based upon the scientific community's consensus on zinc, the plaintiff argued that her general causation burden was satisfied—she relied

[119] The Court's best guess is that Dr. McTiernan places high reliance on dietary and occupational studies. *See infra* Section VI(A)(4)(a). Dr. Moorman expressly relies upon several dietary studies and Hidajat to the exclusion of most ranitidine epidemiology. *See infra* Section VI(A)(4)(b). Dr. Salmon uses dietary and occupational studies as the foundation of his dose-response relationship analysis. *See infra* Section VI(B).

upon studies about zinc to prove general causation for Fixodent, which contained zinc. *Id.* at 1303-06.

Both the district court and the Eleventh Circuit disagreed, finding that the Plaintiff had a burden to show that Fixodent—not zinc, generally—could cause her neurological damage. *Id.* at 1303-04 ("[T]he district court properly determined that Fixodent, containing zinc, was in *McClain* category two [which is where] . . . . the medical community generally does not recognize the substance in question as being toxic."). Viewed in that light, the Fixodent plaintiff lacked evidence on "**how much <u>Fixodent</u> must be used**" for an increased risk of neurological damage. *Id.* at 1307 (emphasis added). This Court, finding *Chapman* persuasive, disagrees with the Plaintiffs' contention that it is NDMA—not ranitidine—that should be the Court's focus. *See also Burst v. Shell Oil Co.*, No. CIV.A. 14-109, 2015 WL 3755953, at *10 (E.D. La. June 16, 2015) (rejecting a plaintiff's reliance on literature on benzene exposure in general in lieu of literature on gasoline exposure, which contains benzene), *aff'd*, 650 F. App'x 170 (5th Cir. 2016); *Henricksen v. ConocoPhillips Co.*, 605 F. Supp. 2d 1142, 1156 (E.D. Wa. 2009) ("This is a product's liability action and Defendant's product is gasoline. It is undisputed that Henricksen's exposure was to the mixture gasoline, not simply to the substance benzene."). Instead, a critical causation inquiry is how much ranitidine must be used for an increased risk of cancer: what is the dose-response relationship? On this critical question, the attenuation of the dietary and occupational studies becomes evident.

The amount of NDMA in ranitidine is uncertain. A critical, important benefit of the ranitidine epidemiology is that it removes this question from the estimate of cancer risk. Regardless of how much NDMA was in ranitidine products at the time of manufacture, people consumed them. Regardless of how much NDMA was formed in ranitidine products through

exposure to heat in the supply chain, people consumed them. Did that consumption, regardless of how much NDMA was in the ranitidine over time, result in cancer? Relatedly, did anyone who consumed ranitidine get cancer, regardless of how long their ranitidine consumption lasted? These are the narrowed (and highly relevant) questions that ranitidine epidemiology attempts to answer. In contrast, the relevance of dietary or occupational studies on NDMA to this litigation is contingent not only upon how much NDMA was in ranitidine, but also on how long people consumed ranitidine.

The concept of how long a plaintiff must use a product to reach toxicity was present in *Chapman* with Fixodent. There, the plaintiff failed to meet her general causation burden not only because she lacked evidence on how much Fixodent must be used for toxicity, but also "how *long* [to] increase the risk of" toxicity. *Id.* at 1307 (emphasis added). Just as in *Chapman*, there are problems in this MDL with the Plaintiffs' attempts to show how, and when, ranitidine consumption causes cancer, and this difficulty is particularly problematic in the context of dietary and occupational studies.

Dietary questionnaires assume a lifetime worth of unaltered dietary consumption. The Plaintiffs' occupational study assumed continued exposure to NDMA in a factory. To compare many decades of food consumption or factory exposure to ranitidine, one would have to have some amount of quantifiable time of ranitidine consumption to create a comparison. Yet this is an issue that the Plaintiffs' experts disavow an opinion on,[120] instead calling it a question that cannot be answered:

> Q. Okay. So for purposes of this analysis, you assumed that ranitidine patients were taking the levels that you took from the FDA analysis on a chronic basis over many years; is that right?
>
> . . . .

[120] Dr. Salmon attempts to answer the question of how long one must consume ranitidine to develop cancer. The Court addresses his threshold dose and dose-response analysis in Section VI(B), *infra*.

> A. So what I am saying here is that the pattern of exposure to NDMA through dietary intake is comparable to people who take ranitidine on a chronic basis, and the point above that was that the levels that the FDA—you know, they described it qualitatively as the amounts found in many of the ranitidine products was probably to levels in grilled or cooked meats. So I think that is—you know, that's the statement of my opinion.
>
> Q. Tell me what you mean when you say, "chronic basis over many years." Define that for me.
>
> A. Again, when one thinks about how acid-suppressant drugs are taken by many people, chronic would be on a long-term—you know, on daily or long-term basis and over a period of many years. It's—**I can't quantify many, many years**, but, you know, it is apparent from some of the data that I cited that many people, you know, will take them for a long, long time.
>
> Q. And when you say many years, what did you have in mind? Ten years? Less than ten years? More than ten years? . . . .
>
> A. **Again, I think that anybody would not be able to quantify many**. It's—you know, again, it's—some people take them five years, ten years, even longer. So those are the kind of uses—the patterns of use that I was trying to get at in that statement.

Moorman Dep. at 500-02 (emphasis added). Thus, in addition to the average *amount* of NDMA in ranitidine being a highly disputed fact subject to uncertainty, the *timing* of ranitidine carcinogenicity is also unknown or uncertain. Without knowing how long ranitidine users take ranitidine, one cannot calculate their lifetime intake of NDMA. And without knowing the lifetime intake of NDMA through ranitidine, one cannot reliably compare a lifetime of NDMA consumption through ranitidine to a lifetime of NDMA consumption through food or rubber factory labor. In other words, if the yardstick the Plaintiffs' experts wish to use is a lifetime of food consumption, they must have some time period of ranitidine consumption to measure against it. This they do not have, as they disavow opinions on the issue.

The Plaintiffs' experts base their opinions in large part on dietary and occupational studies; studies that require ranitidine to NDMA conversions on the timing and frequency of NDMA

consumption. They have no opinions on timing or frequency, leaving analytical gaps in their expert opinions. At some point it falls to this Court, as a *Daubert* gatekeeper, to conclude that an expert's analytical leap is simply too great from the available data to the expert's conclusion. *See Chapman*, 766 F.3d at 1305-06. Here, like *Chapman*, the leap that the Plaintiffs' experts must make from the dietary and occupational studies to the causation question in this MDL is too great.

Third and finally, for the lifetime-based dietary and occupational studies to be part of a reliable methodology, an expert would have to account for the historical amount of NDMA in ranitidine. The historical amount of NDMA in ranitidine is a necessary part of any comparison between a lifetime's worth of NDMA through ranitidine consumption and a lifetime's worth of NDMA through eating food or working in a factory.

The Plaintiffs' experts assume that the amount of NDMA detected in ranitidine in the present was also the amount of NDMA in ranitidine in the past. But the Plaintiffs' experts concede that they have no data to make any conclusions about historical ranitidine NDMA levels:

> Q. And you are aware that Zantac was on the market for around 30 years; is that right?
>
> A. Yes, I am aware that it has been on the market since the early 1980s, if I'm recalling correctly.
>
> Q. You are.
>
> A. Okay.
>
> Q. Are you aware of any data showing NDMA levels that were detected in any ranitidine pills before 2019?
>
> A. When considering that, one has to think were they looking for it. So was the testing actually performed. But on the basis of what is expected as the source of the ranitidine—I'm sorry—the source of the NDMA in the ranitidine products, that it is a breakdown of the ranitidine molecule resulting in the formation of NDMA. So even though it would not—there may not have been measures of NDMA from the 1980s, based on the source, what is thought to be the source of NDMA in ranitidine

tablets, one would expect that that would have been apparent in the 1980s, 1990s, and up to when it was withdrawn from the market.

Q. That really wasn't answering my question. All I really wanted to know is do you have test results of—related to NDMA in ranitidine pills during the 1980s, 1990s, or 2000s?

A. Okay. And I do not have those test results. But again, I think that the statement that I made based on what is thought to be the source of NDMA in ranitidine tablets, that it's a very reasonable assumption to say that the levels done in testing in current years would be similar to what would have been found if the testing had been done back then.

. . . .

Q. And if I understand your methodology, you took those test results from 2019 and made certain assumptions that similar levels were in all ranitidine pills going back to the 1980s. Is that fair?

A. Well, again, I am going back that assumption—I made that assumption, but I think that it is a valid assumption, once again, for the point that I made, that the source of the NDMA is not thought to be an exogenous contaminant but a breakdown product of the NDMA molecule. So it's a very reasonable assumption, I believe.

Q. Now, have you seen this methodology replicated anywhere in the peer-reviewed medical literature where someone is trying to correlate NDMA levels in food to NDMA levels in ranitidine or any other drug?

A. Well, I think that the statement that I quoted that the FDA said the amount of NDMA in ranitidine products was comparable to levels in grilled or smoked meats, so I think that I do—you know, the FDA made that statement. That was not an extrapolation that I made. I took it from what the FDA said.

Q. Okay. Do you know whether anyone else has done what you've done, that is, try to correlate the levels of NDMA in food to the levels of NDMA detected in ranitidine over the course of 30 years? . . . .

A. You know, I have to go back to—the testing was done recently, but there is not any reason to think that the breakdown of the ranitidine NDMA would have been different ten years ago, twenty years ago, or longer. It is—you know, it's a result of the instability of the ranitidine molecule is how I understand it.

Moorman Dep. at 503-07.

Without factual support for an assumption, an expert's opinion becomes a "leap of faith" prohibited by *Daubert*. *Rink*, 400 F.3d at 1292. Relatedly, an expert may not make assumptions based upon conjecture. *Id.* By way of example, in *Rink v. Cheminova, Inc.*, an expert assumed that temperature data from Texas could be used for calculations in Georgia. 400 F.3d at 1292. The expert's assumption was based upon his reasoning that, because Texas and Georgia are in roughly the same latitudinal range, the temperature data for Texas would approximate temperature data in Georgia. *Id.* The district court disagreed, and the appellate court affirmed, because the "[t]ransposition of data based on such conjecture and rough approximation lacks the 'intellectual rigor' required by *Daubert*." *Id.*

Like *Rink*, the assumption that NDMA levels in the present would equal NDMA levels in the past is conjecture that "lacks intellectual rigor" for three reasons.[121] First, the Plaintiffs' own theory of the case is that the amount of NDMA in ranitidine is highly variable, depending on the specific conditions that a batch of ranitidine encounters throughout its product lifespan. Second, the Plaintiffs' own internal data shows variability in the amounts of NDMA in ranitidine, across manufactures, lots, time frames, and consumer-specific conditions. *See supra* Section V(A)(1)(e). The FDA's data also shows substantial variability. Salmon Report at 212. Third, in recognition that the quantification of NDMA requires "intellectual rigor" and expert analysis, the Plaintiffs specifically retained Dr. Najafi to quantify the amount of NDMA in ranitidine and to study ranitidine's properties.

In light of the Court's decision to exclude the expert opinion of Dr. Najafi, the Plaintiffs lack a reliable expert opinion on the quantification of the amount of NDMA in ranitidine. Based

[121] The Court does not mean to suggest that it would be conjecture for an expert to conclude that the chemical properties of ranitidine in the past are the same as the chemical properties of ranitidine in the present. Rather, the Court's focus is on the quantification of NDMA in ranitidine for several decades in the past based upon a small number of tests in the present, without any further analysis, data, or discussion on the topic.

upon its review of the record in the totality and the Plaintiffs' epidemiological experts' assumptions on the matter, the Court concludes that the experts' assumptions on the historical quantification of NDMA in ranitidine amount to speculation and conjecture.

In sum, the Court agrees with the Defendants that any expert's reliance upon the dietary and occupational studies discussed above to form a general causation opinion on ranitidine amounts to an unreliable methodology.

All Other Studies Relied Upon by the Plaintiffs' Epidemiology Experts

The Court addresses one final matter. As attenuated as the relevance is for dietary and occupational studies that focus on NDMA in lieu of ranitidine, the Plaintiffs' experts rely upon studies that are even less relevant and even more attenuated. For example, the Plaintiffs' experts rely upon studies of water, vegetables, processed meat, and fertilizer that did not study ranitidine and did not study NDMA. Instead, those studies focus on molecules (such as nitrites and nitrates) that could, under certain circumstances, form NDMA. The Court deems the size of the analytical gap between the data in those studies and the facts of this case to be self-evident and to not warrant further discussion here.

4. Defendants' Specific Challenges to Plaintiffs' Epidemiology Experts

In addition to their generalized challenges, which cut across multiple expert opinions, the Defendants make specific arguments targeted towards specific experts' opinions. The Court first examines two of the Plaintiffs' expert opinions: (a) Dr. McTiernan and (b) Dr. Moorman. The Court then addresses (c) a supplemental amendment to those experts' reports that the experts completed after the Court heard oral argument on the Defendants' *Daubert* Motions. The Court finally turns to the remaining Plaintiffs' experts who offered epidemiological opinions: (d) Drs.

Salmon, Michaels, and Le, and (e) Dr. Hidajat. When applicable, the Court applies its more generalized rulings from Section VI(A)(3), *supra*, to specific expert's opinions.

a. **Dr. McTiernan**

Dr. McTiernan is the Plaintiffs' first of two retained epidemiologists. Dr. McTiernan's official opinion is that the "use of ranitidine can cause cancer." McTiernan Report at 16. The Defendants argue that Dr. McTiernan fails to employ a reliable methodology in her evaluation of the various epidemiological studies. The Defendants essentially criticize every input into Dr. McTiernan's analysis in that they attack every study that Dr. McTiernan utilizes. In response, the Plaintiffs argue that Dr. McTiernan's opinion is appropriately sourced in her appraisal of all available epidemiology.

Dr. McTiernan relies upon ranitidine epidemiology, dietary epidemiology, occupational studies on NDMA, and other non-ranitidine, non-NDMA studies to support her general causation opinion. As discussed in Section VI(A)(3)(a), however, Dr. McTiernan does not rely upon the *conclusion* of any study to support her opinion that ranitidine causes cancer, because no published study has ever reached that conclusion. Instead, Dr. McTiernan relies upon specific data embedded within various studies to support her opinion.

After extensive review of the specific data that Dr. McTiernan relies upon, the Court makes the following observations: (i) Dr. McTiernan routinely disregards the relative risk of ranitidine use compared to the use of other acid suppression medications (active comparators) in ranitidine epidemiology, and she also disregards the concept of statistical significance; (ii) Dr. McTiernan does not clarify which studies she relies upon, and she omits the weight she assigns to the studies she relies upon; and (iii) Dr. McTiernan's analysis in this litigation departs from conventional scientific standards and from her own summary of those conventional scientific standards. After

explaining its three observations above, the Court (iv) rules on the admissibility of Dr. McTiernan's expert opinion.

i. Active Comparators, Statistical Significance, and Ranitidine Epidemiology

The Court observed above that Dr. McTiernan routinely disregards the relative risk of ranitidine use compared to the use of other acid suppression medications (active comparators) in ranitidine epidemiology, and she also disregards the concept of statistical significance. This observation is based upon the Court's review of the ranitidine studies that Dr. McTiernan relies upon in forming her general causation opinion. To explain the Court's synthesis of Dr. McTiernan's analysis, the Court summarizes below the various ranitidine studies that feature into Dr. McTiernan's general causation opinion.

Bladder Cancer Studies. Dr. McTiernan deems four[122] ranitidine studies "informative" for bladder cancer. McTiernan Report at 199. Those studies are: Yoon, Kantor, Nørgaard, and Cardwell. She relies upon the studies for the proposition that "the increased risk in ranitidine users vs. nonusers ranged from 10% to 41%." *Id.*

For Yoon, the risk rate was indeed at the upper end of Dr. McTiernan's range: 41%. Because the risk rate of 1.41 was accompanied with a confidence interval of .88 to 2.24, however, the risk rate utilized by Dr. McTiernan was not statistically significant. Yoon et al., *supra*, at 5. Even so, if Dr. McTiernan intends to rely upon this 41% figure (the Court addresses Dr. McTiernan's lack of transparency in Section VI(A)(4)(a)(ii), *infra*), it would contravene her

[122] Dr. McTiernan references a fifth study, Iwagami, on page 199 of her report, however, based upon the Court's review of Dr. McTiernan's report and the fact that Iwagami did not report any risk rates for bladder cancer, the Court does not believe that Iwagami was intended by Dr. McTiernan to be an additional, fifth study that factored into her analysis. Dr. McTiernan also references a sixth study, McDowell, but the word "bladder" does not even appear in the McDowell study. The Court believes that Dr. McTiernan references the McDowell study in error because it utilized the same database as Cardwell, which did study bladder cancer. Finally, Dr. McTiernan references a seventh and eighth study, Michaud and Habel, but, as those studies comingled drugs and cancers in their results, the Court does not see how those studies could qualify as one of Dr. McTiernan's "informative" studies. *See supra* note 84 and the Court's discussion of Habel on pancreatic cancer in this section, *infra*.

statement that her ascribed range of 10% to 41% was for use versus non-use, as Yoon reported active comparator results. *See id.*

For Kantor, the risk rate was 1.22, compared to non-users.[123] Kantor et al., *supra*, at 1856. This risk rate does fall within Dr. McTiernan's ascribed range, but it was not statistically significant with a confidence interval of .74 to 2.01. *Id.*

For Nørgaard, it is unclear what figure Dr. McTiernan relies upon as she references many different findings in the study and does not elaborate on which finding she finds the most important to her analysis. At times Dr. McTiernan discusses a crude, unadjusted risk rate of 33% that compared ranitidine use to the use of other H2-blockers. McTiernan Report at 125, 184, 318. This crude figure did not form the basis for the study authors' conclusion, and it would be puzzling to this Court for Dr. McTiernan to rely upon a crude, unadjusted, risk rate. At other times Dr. McTiernan discusses an adjusted 11% risk rate that was not statistically significant, and which also compared ranitidine use to the use of other H2-blockers. *Id.* Finally, Dr. McTiernan also discusses a 24% risk rate that was statistically significant and compared ranitidine use to PPI use. *Id.*

Thus, Dr. McTiernan either relies upon a crude, unadjusted risk rate of 33% without explanation for this reliance, an adjusted but statistically insignificant risk rate of 11% based upon an H2-blocker comparison, or a statistically significant 24% risk rate that was based upon a PPI comparison. The latter two risk rates used an active comparator analysis, which contravenes Dr. McTiernan's ascribed intent to rely upon Nørgaard for a "10% to 41% range" for a use versus non-

[123] Kantor also found a statistically insignificant positive risk rate between ranitidine use and PPI use. Kantor et al., *supra*, at 1857.

use comparison. The Court's best guess is that Dr. McTiernan utilizes a crude, unadjusted risk rate of 33% in rendering her opinion without explanation.[124]

For Cardwell, the study authors found an increased risk of 22% when ranitidine use was compared to non-users. Cardwell et al., *supra*, at 1. That risk was statistically significant. *Id.* Based upon Dr. McTiernan's discussion of Cardwell, the Court believes that this risk rate is the one upon which she relies. McTiernan Report at 185-86. Notably, Dr. McTiernan expressly acknowledges the statistical significance of the risk rate. *Id.* at 201. But in her discussion of Cardwell Dr. McTiernan makes no mention, and does not recognize or credit, the fact that the Cardwell authors found no statistically significant association between ranitidine and bladder cancer when ranitidine users were compared to the users of other H2-blockers. Cardwell et al., *supra*, at 6. Additionally, the Cardwell study did not compute a statistically significant risk rate when the researchers looked for evidence of a dose-response relationship, as compared to users of H2-blockers and users of PPIs. *Id.* Dr. McTiernan's discussion of Cardwell is silent on this point.

In summary, Dr. McTiernan relies upon bladder cancer ranitidine epidemiology with statistically insignificant data and non-user comparison data. She does not provide study-specific explanations for her reliance on that data. Additionally, it is possible that Dr. McTiernan relies upon crude, unadjusted data in Nørgaard.

Esophageal Cancer Studies. It is possible that Dr. McTiernan does not rely upon any ranitidine epidemiology to form her general causation opinion on esophageal cancer. On page 219 of her report, in the context of her final analysis, she states: "Few studies have examined the association between ranitidine use and risk of esophageal cancer, and they all had serious flaws."

[124] At oral argument, the Court gave the Plaintiffs the opportunity to clarify which numbers Dr. McTiernan relies upon in Nørgaard. The Plaintiffs' clarification did not enlighten the Court. *See* Defendants' Sept. 22 *Daubert* Hearing Tr. at 18-20.

The Court is uncertain about Dr. McTiernan's reliance, however, because in her analysis of esophageal cancer she credits data in a ranitidine study, Adami. *Id.* More specifically, she characterizes an Adami crude risk rate of 1.34 and a statistically insignificant risk rate of 1.71 for long-term users of ranitidine that developed squamous cell carcinoma as "especially significant." *Id.* Dr. McTiernan considers this data to be especially significant because the Adami study "had several limitations that biased relative risks towards the null." *Id.*

The Court notes that the 1.34 crude risk rate is not mentioned in the text of the study itself; it is included in supplementary tables distributed in conjunction with the study. *Id.* at 13. The statistically insignificant 1.71 risk rate cited by Dr. McTiernan was based upon only 8 cases of one subtype of esophageal cancer, and, when that subtype was combined with other forms of esophageal cancer, the combined risk rate was a statistically insignificant rate of 1.16 (confidence interval .8 to 1.69). *Id.* at 5.

There is a facial inconsistency in Dr. McTiernan's reliance upon the two risk rates referenced above. Dr. McTiernan relies upon the long-term risk rate for squamous cell carcinoma (a type of esophageal cancer), but she does not rely upon the long-term risk rate for esophageal cancer, generally. If Dr. McTiernan had relied upon the long-term risk rate for esophageal cancer generally, just as she does for squamous cell carcinoma, she would have utilized a statistically insignificant rate of 1.16 instead of her cited (crude) risk rate of 1.34. *Id.* at 5. Relatedly, while Dr. McTiernan relies upon the crude risk rate for esophageal cancer, generally, she does not rely upon the crude risk rate for squamous cell carcinoma. If Dr. McTiernan relies upon the crude risk rate for squamous cell carcinoma, just as she does for esophageal cancer, generally, she would utilize a statistically insignificant risk rate of 1.21 instead of her cited risk rate of 1.71. *Id.* at 13.

Why weren't all crude risk rates "especially significant," and why weren't all long-term ranitidine risk rates "especially significant"? Dr. McTiernan does not explain this, but assuming Dr. McTiernan did credit select data in the Adami study for her ultimate opinion, it would appear to this Court that Dr. McTiernan selected higher risk rates that numerically fit her conclusion in lieu of selecting risk rates based upon an evenly applied, objective criteria.

In her final analysis, Dr. McTiernan makes no mention of the ultimate conclusion of the Adami study authors, who found "no compelling evidence that ranitidine increases the risk of upper gastrointestinal cancer," nor does she confront the fact that the final adjusted risk rate in Adami was not statistically significant (comparing ranitidine to both H2-blockers and PPIs). *Id.* at 1. Finally, Dr. McTiernan does not credit or rely upon the Kim Y study, which found a statistically significant decrease in the risk of esophageal cancer when ranitidine use was compared to the use of other H2-blockers. Kim Y et al., *supra*, at 606.

In summary, at best, Dr. McTiernan relies upon a crude, unadjusted relative risk in one study, together with a selected, statistically insignificant relative risk for one subtype of esophageal cancer.

<u>Liver Cancer Studies</u>. In her final analysis, Dr. McTiernan lists five different liver cancer studies that reported on ranitidine use: Adami, Kantor, Kim Y, Tran, and Yoon. McTiernan Report at 233. She states that in two of these five studies, the risk of ranitidine use versus non-use ranged from 41% to 91%. *Id.* Dr. McTiernan does not specify which two of the studies reported this range. *Id.* She states that "all likely underestimated [sic] amount of ranitidine used." *Id.* The Court summarizes the results of the five studies for liver cancer to discern which studies form the basis for Dr. McTiernan's opinion.

The Adami, Kim Y, and Yoon studies examined liver cancer. Each study compared ranitidine users to users of H2-blockers. In Adami, the authors computed a risk rate of .79.[125] Adami et al., *supra*, at fig.1. In Kim Y, the authors computed a risk rate of .69. Kim Y et al., *supra*, at 606. And in Yoon, the authors computed a risk rate of .39. Yoon et al., *supra*, at 5. Because all of these studies ascribed a protective effect to ranitidine—the risk rates were all below 1—and because each study used an active comparator analysis, the Court does not believe that Dr. McTiernan relies upon any of these studies for her causation opinion.

The Court did not previously summarize the Tran study because it was completed before the FDA's initiation of a voluntary recall of ranitidine. Perhaps because of its earlier inception, the Tran study's primary focus was on PPIs, not H2-blockers. K. T. Tran, *Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use and Risk of Liver Cancer in Two Population-Based Studies*, 48 Alimentary Pharmacology & Therapeutics 55, 55 (2018). The Tran study only compared ranitidine users to non-users; it did not include an active comparator analysis for ranitidine specifically. *Id.* at 61. The Tran study used two different databases. *Id.* at 55. One database was the Primary Care Clinical Informatics Unit, the same database used in Cardwell. *Id.* The other database was the UK Biobank, the same database used in Kantor. *Id.* at 51.

As to the Primary Care database, the study authors computed a relative risk rate of 1.41 with a confidence interval of .91 to 2.15. *Id.* at 60. Using the UK Biobank database, the study authors computed, based upon 8 cases of liver cancer, a relative risk rate of 1.82, with a confidence interval of .87 to 3.79. *Id.* at 61. Based upon these statistically insignificant results, the study authors concluded: "[T]here was little evidence of association with use of H2-blockers." *Id.* at 5.

[125] There is some indication on page 228 of Dr. McTiernan's report that she credited the crude, unadjusted risk rate in Adami of 1.13, however, because this risk falls below Dr. McTiernan's ascribed range of 41% to 91%, the Court's best guess is that Dr. McTiernan did not rely upon the results of the Adami study.

No dose-response relationship information for ranitidine is available in the study. Because this study had a range of positive associations closely mirroring the range referenced by Dr. McTiernan, the Court believes Dr. McTiernan relied upon this study in forming her general causation opinion.

Finally, the Kantor study considered liver cancer. Comparing ranitidine users to non-users, the authors computed a statistically significant relative risk rate of 1.91. Kantor et al., *supra*, at 1857. As compared to PPI users, however, the risk rate decreased to a statistically insignificant 1.15, with a confidence interval of .58 to 2.26. *Id.* Because the 91% risk rate for non-user comparisons corresponds to the upper range of the risk rates referenced by Dr. McTiernan in her Bradford Hill analysis, the Court believes that the Kantor study qualifies as the second study (of two) that Dr. McTiernan relies upon for her conclusions.

In summary, the Court believes that Dr. McTiernan relies upon the statistically significant Kantor risk rate of 1.91, comparing ranitidine users to non-users, in lieu of the statistically insignificant Kantor risk rate of 1.15, comparing ranitidine users to H2-blocker users. The Court also believes that Dr. McTiernan relies upon the statistically insignificant risk rates in Tran, which compared ranitidine users to non-users, and which did not conduct an active comparator analysis.

Pancreatic Cancer Studies. Dr. McTiernan's final analysis for pancreatic cancer references three ranitidine epidemiological studies: McDowell, Iwagami, and Habel. McTiernan Report at 250. Dr. McTiernan cites to these studies for the proposition that "risk for users versus non-users increased in two of these three studies" and "one found more than doubling or [sic] risk and one found a 37% increased risk for pancreatic cancer." *Id.* at 251. Because Dr. McTiernan does not specify which two of the three studies she relies upon, the Court summarizes all three studies.

The Court has not previously discussed the Habel study for three reasons. First, the Habel study predated the FDA's voluntary recall of ranitidine. Perhaps due in part to the timing, the Habel study was designed to measure the cancer risk of another drug, cimetidine, not ranitidine. Laurel A. Habel et al., *Cimetidine Use and Risk of Breast, Prostate, and Other Cancers*, 9 Pharmacoepidemiology & Drug Safety 149, 149 (2000). Ranitidine users were utilized in Habel as active comparators for cimetidine users. *Id.* Second, because ranitidine was not the focus of the Habel study, the authors reached no conclusion, and indeed engaged in no discussion, about whether ranitidine causes cancer or is associated with cancer. Third, the Habel study commingled Designated Cancers in this MDL, such as esophageal cancer and stomach cancer, rendering an individual risk estimate for either one of those cancers impossible. *Id.* at 151.

Pancreatic cancer was the only Designated Cancer in Habel that was studied independently. *Id.* For pancreatic cancer, based upon a comparison of ranitidine use versus non-use, the study authors computed a relative risk of 2.60, with a confidence interval of 1.06 to 6.38. *Id.* This very large confidence interval is a result of the fact that the Habel authors only identified five cases of ranitidine users who developed pancreatic cancer. *Id.* Because so few ranitidine cases were studied in Habel, the Court turned to Dr. McTiernan's deposition testimony to see if Dr. McTiernan did indeed rely upon the Habel data:

> Q. So let's cut to the chase here, Dr. McTiernan. You see the pancreatic finding of 2.60 for ranitidine?
>
> A. Yes.
>
> Q. Do you see that it's based on five cases?
>
> A. Yes.
>
> Q. Are you relying on that finding for your opinions about pancreatic cancer and ranitidine in this case?

A. I've reviewed it, I've referenced it in my report, and what I don't know is what I said about it in the report.

Q. Okay. I understand that you don't know what you said about it in the report, but my question is, are you relying on that finding for your opinions in this case.

A. I mention my report because that's where my opinions are written down, and so the issue of reliance is what I surmised and what I've concluded in my report.

Q. And sitting here today, you can't tell me one way or the other whether you are relying on this finding for pancreatic cancer in the Habel study?

A. I know that I referenced it, I know that I reviewed this paper. I can't recall without looking through my report exactly what I stated in terms of this paper and my opinions.

Q. Would you reach conclusions about an association between ranitidine and pancreatic cancer based on a finding that has—based on a risk estimate that is based on only five exposed cases?

A. It depends on the study. It's a small number of cases, but it depends on the study, on what conclusion I would make.

Q. We know the study now, right? It's not a secret what the study is, it's a Habel study.

A. Yes.

Q. So –

A. I'm sorry, I'm sorry. The question sounded like a general question.

Q. No, it's not a general question at all. I'm saying in this study, you have a risk estimate for pancreatic cancer of 2.60 that is based on five exposed cases; correct?

A. That's what they have, yes.

Q. Okay. And are you drawing any inferences about an association between ranitidine and pancreatic cancer from that risk estimate?

A. And this is why I need to look at my report and see what—what I wrote and what I considered in my final analyses for pancreatic cancer.

Q. But sitting here today, you cannot tell me, right? You cannot tell me whether or not you are relying on that risk estimate for pancreatic cancer for your opinions.

> A. I cannot tell you what I wrote in my report without reading my report about how I—how I considered this paper in my final analysis for pancreatic cancer.

McTiernan Dep. at 377-80. Dr. McTiernan thus points the Court to her report, but Dr. McTiernan includes little discussion of Habel in the pancreatic cancer section of her report. McTiernan Report at 243. Nonetheless, because the Habel 2.60 risk rate is a "more than doubling" of the risk of cancer, and because Dr. McTiernan includes Habel in the list of studies that she cites for that proposition, the Court concludes that Dr. McTiernan does rely upon the five pancreatic cancer cases in the Habel study as part of her general causation opinion.[126]

As to Iwagami, that study did focus on pancreatic cancer, but it only identified 93 ranitidine or nizatidine users who developed that cancer. Iwagami et al., *supra*, at 1, 6. Perhaps because of the limited data, the Iwagami authors did not report risk rates for pancreatic cancer or otherwise draw any conclusions. In her discussion of Iwagami, Dr. McTiernan attempts a "crude calculation" of the Iwagami risk rate, but her calculation amounted to .95. McTiernan Report at 242. Thus, the Court does not believe that Iwagami forms a basis for Dr. McTiernan's expert opinion.

As to McDowell, based upon 143 cases, that study did find a statistically significant 37% increase in risk when comparing ranitidine users to non-users. McDowell at el., *supra*, at 5-6. Because this increased risk matches and corresponds to the range listed in Dr. McTiernan's Bradford Hill analysis section, the Court believes that McDowell is the second of two ranitidine studies that Dr. McTiernan relies upon for her pancreatic cancer opinion.

However, the McDowell study authors did not conclude that ranitidine is positively associated with pancreatic cancer because their data did not show evidence of a dose-response relationship. When ranitidine users with the highest number of prescriptions (6 or more) were

[126] The Court notes that Dr. McTiernan calls four cancer cases in another study a "a major weakness." McTiernan Report at 263.

examined, their risk rate was *reduced* to a statistically insignificant 1.24, with a confidence interval ranging from .91 to 1.69. *Id.* at 5. By contrast, those who obtained the fewest number of ranitidine prescriptions (5 or less) had a higher risk rate of 1.49, with a confidence interval ranging from 1.12 to 1.99. *Id.* Based upon this apparent inconsistency, the researchers concluded: "[N]o definitive exposure-response relationship between [ranitidine] and cancer risk was observed," "the association between ranitidine and pancreatic cancer has yet to be determined," and "further studies of the association between ranitidine and pancreatic cancer" should take place. *Id.* at 1, 7.

Dr. McTiernan does not rely upon the findings in Adami or Kim Y. In Adami, comparing ranitidine users to H2-blocker users, the study authors computed a risk rate of .81, Adami et al., *supra*, at fig.1, and in Kim Y, also comparing ranitidine users to H2-blocker users, the study authors computed a risk rate of .54, Kim Y et al., *supra*, at 606. Finally, for comparison purposes to the five pancreatic cancer cases in Habel, the Kim Y study was based upon 320 cancer cases, *id.* at 608, 610, and the Adami study was based upon 517 cancer cases, Adami et al., *supra*, at 19.

In summary, for pancreatic cancer, the Court believes that within the field of ranitidine epidemiology, Dr. McTiernan relies upon the statistically significant data in McDowell and Habel that compared ranitidine users to non-users.

Stomach Cancer. In her final analysis, Dr. McTiernan states that "[a] total of 8 studies looked at associations between ranitidine use and risk of stomach cancer." McTiernan Report at 280. She concludes that six of those studies found a higher risk of stomach cancer when comparing ranitidine users to non-users. *Id.* According to Dr. McTiernan, the increase in risk "rang[ed] from 6% (relative risk 1.06) to more than doubling (relative risk 2.42)." *Id.* At least in her conclusion section, Dr. McTiernan provides no further insight as to the studies that forms the basis of her

general causation opinion. The Court therefore examines the eight studies Dr. McTiernan references to discern the six studies upon which Dr. McTiernan relies.

In the stomach cancer section of her report, Dr. McTiernan discusses the Adami study a great deal. Although she does not reference the study authors' conclusion ("no compelling evidence that ranitidine increases the risk of upper gastrointestinal cancers," Adami et al, *supra*, at 3) or the authors' final, adjusted risk rates for stomach cancer, she does discuss the study's crude, unadjusted risk rate numbers for stomach cancer, which ranged from a statistically insignificant .88 to a statistically significant 1.28 for "unknown" stomach cancers. McTiernan Report at 259 (citing Adami et al., *supra*, at supplementary fig.1).

Missing from this discussion in Dr. McTiernan's report is the study authors' conclusion on continuous prescription refills: "We found no evidence of an increase in risk with a larger number of prescriptions; on the contrary, [risk rates] remained clustered around 1.0 in comparisons with other [H2-blockers] and with PPIs, and no single [risk rate] was statistically significant." Adami et al., *supra*, at 114. Based upon the volume of discussion in her report and Dr. McTiernan's reliance upon crude, unadjusted numbers for other cancers, the Court believes that Dr. McTiernan relies upon the statistically insignificant crude, unadjusted numbers in Adami for her general causation opinion—that the Adami study is one of the six ranitidine stomach cancer studies upon which Dr. McTiernan relies.

Dr. McTiernan also devotes considerable discussion to the Kim Y study in the stomach cancer section of her report. However, because that study concluded that the risk rates for stomach cancer were below 1.0—ranging from .49 to .93—the Court does not believe that Dr. McTiernan relies upon the Kim Y study. The Kim S study receives a similar amount of discussion in the report as the Kim Y study, but as that study found a statistically insignificant risk rate of 1.01

comparing ranitidine use to non-use, the Court also does not believe that the Kim S study is a basis for Dr. McTiernan's general causation opinion.

Dr. McTiernan briefly discusses the Kumar study. McTiernan Report at 261. But because that study found that the users of other H2-blockers were far more likely to develop stomach cancer than ranitidine users (83% more likely), the Court does not believe that Dr. McTiernan relies upon the Kumar study in forming her opinion.

Dr. McTiernan discusses the Liu study in her stomach cancer section. The Court has not previously summarized this study for four reasons. First, the purpose and design of the study were not to estimate the risks of ranitidine use. *Id.* at 145 ("[Liu's] primary purpose was to look at associations between use of proton pump inhibitors or H2 blockers in general and risk for stomach cancer."). Accordingly, and second, the study authors expressed no conclusion on ranitidine. Indeed, the word "ranitidine" only appears in the text of the study on two occasions. Third, because ranitidine was not the focus of the study, the study contained no data on a dose-response relationship for ranitidine. *Id.* at 262. Fourth and finally, the data on ranitidine in some areas of the study was extremely limited, with one area of the study computing a relative risk rate based upon four ranitidine users who developed cancer. *Id.* at 263 ("The lack of cases was therefore a major weakness to this second Liu study.").

These limitations notwithstanding, the only risk rate from Liu that Dr. McTiernan cites to in her report is a statistically significant rate of 1.42, comparing ranitidine users to non-users. *Id.* at 262. The Court's best guess is that Dr. McTiernan relies upon this risk rate in formulating her general causation opinion because this risk rate is the only rate she cites from Liu in her stomach cancer conclusion; the risk rate was based upon a comparison with non-users; Dr. McTiernan prefers non-user comparisons; and the risk rate was above 1.

Dr. McTiernan briefly mentions the Iwagami study in her stomach cancer section. *Id.* at 263. Dr. McTiernan cites to a statistically insignificant risk rate of 1.09, with the confidence interval ranging from .92 to 1.17, although she does not acknowledge the authors' conclusion that "there is no significant association between ranitidine/nizatidine and the incidence of cancer diagnosis." Iwagami et al., *supra*, at 9. The Court believes Dr. McTiernan relies upon this number in forming her general causation opinion.

The Yoon study receives a similar amount of discussion in Dr. McTiernan's stomach cancer section as the Iwagami study. Because Dr. McTiernan cites to a statistically insignificant risk rate of 1.06 (confidence interval .86 to 1.31), McTiernan Report at 263, and because that risk rate coincides with the lower end of the range of the 6 studies that Dr. McTiernan relies upon for her opinion, the Court believes that Dr. McTiernan relies upon the Yoon study.

Finally, the eighth study that Dr. McTiernan discusses in the stomach cancer section of her report is the Habel study. There are many reasons why the Court would expect the Habel study would not factor into Dr. McTiernan's analysis. First, the Habel study was designed to measure the cancer risk of another drug, cimetidine, not ranitidine. Habel et al., *supra*, at 149. Ranitidine users were used in Habel as active comparators for cimetidine users. *Id.* Second, because ranitidine was not the focus of the Habel study, the authors reached no conclusion, and indeed engaged in no discussion, about whether ranitidine causes cancer or is associated with cancer. Third, the Habel study comingled esophageal cancer and stomach cancer, **rendering an individual risk estimate for stomach cancer impossible**. *Id.* at 151. Within this comingled data set, only six identifiable ranitidine users developed cancer, resulting in a comingled risk rate of 2.42. *Id.* But because of the small sample size, this risk rate was accompanied with a large confidence interval, ranging from 1.07 to 5.49. *Id.* Yet because the 2.42 risk rate is at the upper range of the 6 studies that Dr.

McTiernan describes as showing a strength of association between ranitidine use and stomach cancer, the Court concludes that Dr. McTiernan relies upon the Habel study in reaching her general causation opinion on stomach cancer.

In summary, the Court believes that Dr. McTiernan relies upon Adami, Liu, Iwagami, Yoon, and Habel.[127] More specifically, the Court believes that Dr. McTiernan relies upon the statistically insignificant, crude, unadjusted risk rates in Adami, the statistically significant but limited data in Liu, the statistically insignificant risk rates in Iwagami and Yoon, and the data that comingled stomach cancer with esophageal cancer on six cancer patients in Habel.

Conclusion. The Court's purpose in analyzing the various ranitidine studies above was to explain its observation that: "Dr. McTiernan routinely disregards the relative risk of ranitidine use compared to the use of other acid suppression medications (active comparators) in ranitidine epidemiology, and she also disregards the concept of statistical significance." When Dr. McTiernan was presented with data in a study that compared ranitidine use to non-use, as opposed to ranitidine use to the use of similar medications, Dr. McTiernan always chooses the former over the latter. In no instance does Dr. McTiernan rely upon active comparator results *in lieu of* a comparison of use versus non-use.

In the absence of study data on ranitidine use versus non-use, Dr. McTiernan routinely, and almost exclusively, relies upon statistically insignificant findings, provided those findings are above 1.0. In no instance does Dr. McTiernan credit statistically insignificant findings when those findings are below 1.0.[128] Nor does Dr. McTiernan choose *not* to rely upon findings *because of* the statistical insignificance of those findings. Further and in addition to the Court's observations

[127] Although Dr. McTiernan references six studies—not five—that showed a positive risk rate for ranitidine use versus non-use, the Court has been unable to identify the sixth study.
[128] Dr. McTiernan expressly indicates that she credits data with risk rates above 1.0 and discredits risk rates below 1.0. *E.g.,* McTiernan Report at 145.

on these matters, Dr. McTiernan also relies upon crude, unadjusted risk rates that are derived from as little as four to six cancer cases, and studies that were designed to measure the risk of other drugs—not ranitidine. What Dr. McTiernan does not rely upon are the conclusions of any study author or any risk rate that is below 1.0.

Dr. McTiernan has various reasons for her weighing of the ranitidine studies that go beyond the Court's discussion and pertain to criticisms of study design and the like. The Court does not discuss those criticisms because they are not relevant to the Court's ultimate conclusions in Section VI(A)(4)(a)(iv), *infra*.

ii. Bradford Hill Analysis

As referenced many times in the Court's analysis in Section VI(A)(4)(a) above, the Court has struggled to identify the studies that served as inputs into Dr. McTiernan's final analysis. Dr. McTiernan does not identify many of the studies she weighs or credits by name and her analysis assigns no weight or credit to any particular study. Similarly, outside of Dr. McTiernan's final analysis, in the more general section of her report describing the available data on ranitidine, Dr. McTiernan does not elaborate on how much, if at all, she weighs any particular study. Relatedly, Dr. McTiernan's deposition provided the Court with very little illumination on Dr. McTiernan's analysis and conclusions. The Court has thoroughly reviewed that deposition. Many of the questions posed by the Defendants to Dr. McTiernan are the same questions that the Court had upon reading Dr. McTiernan's expert report, but Dr. McTiernan routinely evaded germane, fair questions that would have clarified how Dr. McTiernan conducts her analysis. The Court addresses the ramifications of its conclusions on these matters in Section VI(A)(4)(a)(iv), *infra*.

iii. Conventional Scientific Standards and Dr. McTiernan's Expert Report

In the Court's section on statistical significance, Section VI(A)(3)(b)(ii), *supra*, the Court observed that the well-established, conventional definition of statistical significance is when, using a 95% confidence interval, the resulting range of possible risk rates does not "cross the 1." Presumably using this conventional definition, in her expert report Dr. McTiernan references statistical significance, and she uses the phrase "statistically significant" when data facially supports her general causation opinion. *E.g.,* McTiernan Report at 252. Indeed, Dr. McTiernan uses the phrase "statistically significant" more than 100 times in her report, underscoring the idea that some data can be statistically significant while other data is not. *See* McTiernan Dep. at 294. Yet the phrase "statistically ***in***significant" (and the like) does not appear once in Dr. McTiernan's 385-page report, and so when Dr. McTiernan relies upon statistically insignificant data she does not acknowledge that the data is, at least pursuant to the conventional definition, not statistically significant.

Before this MDL, Dr. McTiernan characterized statistically insignificant data (under the conventional definition) as statistically insignificant. In *In re Johnson & Johnson Talcum Powder Products Marketing, Sales Practices & Products Litigation* (*In re Talc*), another MDL, Dr. McTiernan authored a 77-page expert report. 509 F. Supp. 3d 116, 130 (D.N.J. 2020). In that report, Dr. McTiernan characterizes studies as either statistically significant or statistically insignificant. McTiernan Dep. Ex. 26 at 41 ("Among the 8 studies which were not statistically significant . . . ."). Dr. McTiernan's opinion in that litigation was expressly based upon risk rates that were statistically significant; she did not ground her opinion on statistically insignificant data. *Id.* at 9 ("I base this opinion on the statistically significant elevated risk estimates . . . ."). In addition to *In re Talc*, Dr. McTiernan has authored published, peer-reviewed studies where she

characterizes data as either statistically significant or statistically insignificant. McTiernan Dep. at 300-08, 312-23.

As an example of Dr. McTiernan's prior usage of the conventional definition of statistical ***in***significance, the Defendants questioned Dr. McTiernan about a published study she authored where she characterized a confidence interval of .90 to 2.29 as evidence of "no association." *Id.* at 308. Dr. McTiernan responded by testifying that, were she to author the study in the present, she would only state "what the relative risk is" and would not characterize the statistical significance of the results. *See id.* To explain the contrast between her views on statistical insignificance in the past and her views in the present, it was Dr. McTiernan's testimony that at some point her understanding of the concept of statistical insignificance changed. *See id.* at 309-10. As for when, precisely, her understanding changed, she was "not sure." *Id.* at 310.

Dr. McTiernan's present-day understanding of statistical insignificance, applicable in this MDL, is that any positive relative risk that is not 1.0 indicates an association "regardless of the results of statistical tests used with the relative risk." McTiernan Report at 28. Similarly, Dr. McTiernan considers any relative risk to be evidence of an association "regardless of what confidence intervals are calculated." *Id.* at 31. An extreme example of Dr. McTiernan's understanding in practice is found in the context of a discussion on a dose-response relationship on page 278 of her report, where she cites to a study on well water for the proposition that "[r]isk of stomach cancer was increased by 50% in those whose municipal water nitrate level was > 10 mg/L." The relevant data table is displayed below:

Table 1.—Estimated Odds Ratios Obtained through Matched-Pair Analysis

Exposure*	Discordant pairs†	OR(MP)	95% CI
> 0.5	207/226	0.92	(0.75, 1.12)
> 2.5	113/117	0.97	(0.74, 1.35)
> 5.0	25/29	0.86	(0.69, 1.08)
> 10.0	6/4	1.50	(0.12, 18.25)
Private well	120/100	1.09	(0.82, 1.47)

*Expressed in mg/l NO_3-N.
†Number of matched pairs for which control was exposure-negative and case was exposure-positive/number of pairs for which control was exposure-positive and case was exposure-negative.

Witte Report at 29. From this table, one can observe that when the subjects' exposures to nitrates in the well water were .5, 2.5, or 5.0 mg/l, there was no evidence of a dose-response relationship. For each, the risk rate was more or less the same at .92, .97, and .86, respectively. But once the exposure reached 10.0, the risk rate jumped from .86 to 1.5. Thus, Dr. McTiernan cites to this study for the proposition that higher dosages result in higher risk.

The amount of data for each row in the table, however, was not equal. For .5 and 2.5 mg/L, there were hundreds of pairs of subjects for comparison. For 5.0, there were over 50, but for 10.0 there were a mere 10 pairs of subjects for study. Because of this very small sample size, the confidence interval was enormous, ranging from .12 (a reduction in cancer risk of 88%) to 18.25 (an eighteen-fold increase in cancer risk). The sample size generating this confidence interval is not in Dr. McTiernan's report, and Dr. McTiernan does not explain how the grossly imprecise confidence interval may nonetheless be credited in a reliable methodology.

The Court concludes that a methodology that relies upon a confidence interval of .12 to 18.25 as evidence of a dose-response relationship is an unreliable methodology that departs from scientific and mathematical standards. It is one thing to give some consideration towards statistically insignificant data. It is another to abandon the concept of statistical significance completely. Mere speculation by an expert does not satisfy the *Daubert* standard and while the

Court's example above is extreme, it is indicative of Dr. McTiernan's methodology throughout the entirety of her expert report.

Another example of Dr. McTiernan's departure from conventional scientific standards involves comingling data. On page 141 of her expert report, Dr. McTiernan opines that an analysis of cancer risk where all cancers are combined, "is not the accepted method of considering associations of carcinogens with specific cancer type risk." Yet in her final analysis for stomach cancer, Dr. McTiernan relies upon the Habel study, where stomach cancer was commingled with esophageal cancer.[129] Similarly, Dr. McTiernan relies upon the Loh dietary study, which also combines various cancers. McTiernan Report at 15 ("The elevation of risk for all cancer combined is 6% . . . ."). And, in her expert report on page 141, Dr. McTiernan describes the combining of ranitidine users and nizatidine users (as one group for study) as "highly problematic" because of the differing potential of those two drugs to cause cancer. Yet in the context of dietary epidemiology, Dr. McTiernan relies upon studies that looked at processed meats and nitrosamines generally, even though there are many different carcinogens in processed meat and there are many nitrosamines in processed meat besides ranitidine.

In conclusion, the Court believes that Dr. McTiernan's usage of any relative risk rate—regardless of the associated confidence intervals—departs from conventional science and mathematics. The Court also believes that Dr. McTiernan's reliance on commingled data departs from conventional science.

[129] True, Dr. McTiernan may place little weight on the Habel study, but since Dr. McTiernan does not explain how strongly any particular study weighs in her analysis, the Court simply does not know. Similarly, Dr. McTiernan may well place only little weight on the well-water study referenced in the prior paragraph but, again, the Court simply does not know.

iv. Final Ruling as to Admissibility of Dr. McTiernan's Testimony

Below, delineated in **bold**, the Court explains ten reasons why, as a case-specific, fact-specific matter, it deems Dr. McTiernan's methodology to be unreliable. When applicable, the Court discusses the *Daubert* standard and explains how its case-specific conclusions based upon the totality of the evidence fit within the framework of *Daubert* case law.

First, although the primary focus of a *Daubert* inquiry is an expert's *methodology*, this Court is permitted to consider the fact that the Plaintiffs' experts' general causation *conclusions* on ranitidine, including Dr. McTiernan's conclusion, are unique and isolated to this litigation—no independent scientist or publication has concluded that ranitidine causes cancer. Dr. McTiernan's lack of support in the scientific community may be considered by this Court pursuant to one of the core reliability factors delineated in *Daubert*: "Widespread acceptance can be an important factor in ruling particular evidence admissible." 509 U.S. at 594. When considering the widespread acceptance factor, courts have observed that the factor "may seem to be a resurrection of the *Frye* standard (general acceptance in the scientific community)." The Supreme Court's inclusion of the widespread acceptance factor in *Daubert* did just that. *E.g., Allison*, 184 F.3d at 1315. As explained by the Supreme Court in a post-*Daubert* decision, "conclusions and methodology are not entirely distinct from one another." *Joiner*, 522 U.S. at 146. The distinction between conclusions and methodology blurs when experts "extrapolate from existing data" to reach a conclusion, but an extrapolation is akin to a leap over "an analytical gap." *Id.* When the gap is too great—when the leap is too far—a court may exclude an expert's opinion. *Id.*; *see also Lust by & Through Lust*, 89 F.3d at 698 ("When a scientist . . . presents conclusions that are shared by no other scientist, the district court should be wary that the method has not been faithfully applied.").

Because no independent publication or scientist outside of this litigation has concluded that ranitidine can cause cancer, the Court concludes that the Plaintiffs' experts' opinions, including Dr. McTiernan's, not only lack general acceptance in the scientific community, but they also lack any acceptance. When an expert's theory "lacks any acceptance, let alone general acceptance, in the scientific community" it is an indication of an unreliable methodology. *Mirena II*, 341 F. Supp. 3d at 268. Stated differently, no independent scientist or governmental body has made the analytical leap from the existing data as Dr. McTiernan does, and the Court deems this fact to be evidence of an unreliable methodology.

Ranitidine—not NDMA—is at the center of this case. Although the Plaintiffs argue that Dr. McTiernan's opinion may be characterized as an NDMA opinion, an NDMA general causation opinion requires a certain amount of NDMA. Whatever amount of NDMA was in ranitidine, no publication or scientist has concluded, based upon the significant amount of public data available, that the NDMA in ranitidine can cause cancer. Similarly, no independent publication or scientist has concluded that NDMA ingestion from ranitidine may be equated to NDMA inhaled (along with many other carcinogens) in a rubber factory or equated to NDMA ingested (along with many other carcinogens) in processed meat. Those analytical leaps lack widespread acceptance as well.

Almost every scientific study authored since the inception of this MDL—and there have been many—has concluded that there is no evidence of an association between ranitidine and cancer. Even the studies that facially found some evidence of an association exercised great restraint and caution in their conclusions, a far cry from any conclusion that ranitidine causes cancer. Distilled down, the Plaintiffs' experts have no independent, epidemiological scientific support for their conclusions. The Plaintiffs' experts' lack of general acceptance weighs in favor of exclusion. The Court assigns only moderate weight to this factor.

Second, the Court may consider Dr. McTiernan's failure to adequately explain to the Court how her opinion is formulated. An expert's duty to adequately explain his or her opinion and methodology is derived from a core *Daubert* reliability factor: Is the expert's theory capable of being tested? 509 U.S. at 593. Consistent with standard epidemiological practice, Dr. McTiernan uses the well-known Bradford Hill factors to determine whether a perceived association between ranitidine use and cancer was a causal relationship. Those factors consider the various qualities of an observed association, such as the strength of the association, the consistency of the association, and any temporal relationship in the association. In her Bradford Hill analysis, Dr. McTiernan does weigh how strongly the various factors influenced her conclusion (such as assigning high weight to her observation of consistency of an association), but her discussion of the factors is general, brief, and lacking in specificity as to how the data influenced her analysis. By way of example, the Court quotes below an excerpt from Dr. McTiernan's expert report:

> Across the studies of various NDMA exposure, the association between NDMA and risk of liver cancer was highly apparent in more studies than not. As indicated above, the studies included cohort studies from Asia, Europe, and the U.S. Of the 4 ranitidine studies, 3 found elevated relative risks for liver cancer in ranitidine users compared with nonusers; one was statistically significant (e.g., the confidence intervals did not include 1.0). One of the two occupational exposure studies showed elevated liver cancer risk with greater NDMA or precursor nitrate exposure. The one dietary study showed increased liver cancer risk with increased nitrate or nitrite exposure.

McTiernan Report at 236. Dr. McTiernan states that liver cancer risk "was highly apparent in more studies than not." *Id.* at 235. Which studies underpin that statement? What are the "3 of 4" ranitidine studies that showed elevated risks for liver cancer with non-users, and which of those studies most strongly influence Dr. McTiernan's conclusion? What about other data in the "3 of 4" ranitidine studies, such as comparisons between ranitidine users and the users of other H2-blockers? What is the dietary study? Did Dr. McTiernan give equal consideration to ranitidine

studies and dietary studies? Is the "[o]ne of two occupational exposure studies" given the same amount of consideration as the ranitidine studies and dietary study, or is it given more weight? Underpinning all of these unanswered questions is the fact that to conduct a Bradford Hill analysis on data, one must first choose the data to input into the Bradford Hill analysis.

To choose her data inputs, Dr. McTiernan utilizes a weight-of-the-evidence approach whereby she assigns a certain weight to each study she reviews. Yet Dr. McTiernan does not inform the Court, in either her deposition or her expert report, how she weighs the various studies:

> Q: In your expert report, you don't state how you weighed individual studies; correct?
>
> A: That's correct.

McTiernan Dep. at 193. Instead, Dr. McTiernan describes her methodology as follows:

> Q: So you looked at the evidence all together. I just want to understand what you did here. . . .
>
> A: I think I looked at it, all of the—when I was looking at the studies, I looked at the overall design and quality of the studies and identified the strengths and weaknesses for each study and then considered the evidence all together.

Id. at 192.

Because a Bradford Hill analysis looks at the various qualities of a data set—such as strength or consistency—and because a weight-of-the-evidence approach either credits or discounts the data selected for input into a Bradford Hill analysis, courts describe these methodologies as "flexible methodologies." *In re Zoloft*, 858 F.3d 787, 795 (3d Cir. 2017). These methodologies are flexible because they can be implemented in multiple ways. *Id.* Thus, even though as a general matter a Bradford Hill analysis and a weight-of-the-evidence approach are standard practice in epidemiology and can be reliable methodologies, the reality is that every case-specific application of these methodologies "is distinct and should be analyzed for reliability." *Id.*

For a Bradford Hill analysis or a weight-of-the-evidence approach to be reliable, "there must be a scientific method of weighting that is used and explained." *Id.* (quoting *Magistrini*, 180 F. Supp. 2d at 607). Thus, weights must be assigned to data according to a scientific approach. *Id.* at 796 ("[T]he assessment or weighing of that evidence must not be arbitrary, but must itself be based upon methods of science."). Otherwise, the expert may engage in a "conclusion-oriented selection process" *Id.* An expert may engage in a conclusion-oriented process when the expert does not explain the amount of weight that was assigned to each piece of evidence, which may be fairly deemed a "malleable and vague approach" that is "in tension with first principles under *Daubert*, because it makes it all too easy for an expert to manipulate the Bradford Hill factors to support a desired conclusion of causation, and far too hard for an ensuing expert to replicate and rigorously test the expert's analytic approach." *Mirena II*, 341 F. Supp. 3d at 268. It is this difficulty to replicate and test a vague, unexplained weight-of-the-evidence approach that triggers a conflict with *Daubert*.

Dr. McTiernan's expert opinion fails under the foregoing analysis for two reasons. First, the Court cannot even say for certain (for some cancers) what studies influence Dr. McTiernan's ultimate conclusion. Dr. McTiernan does not clearly identify the studies in her expert report or in her deposition. Second, the Court does not know what studies (for any cancer) most strongly influence Dr. McTiernan's opinion. Without this information, the Court cannot say whether Dr. McTiernan selected and weighed studies according to a scientific process. Dr. McTiernan's methodology is "vague and malleable." Dr. McTiernan must explain her methodology in a way that permits the methodology to be tested and vetted for reliability. Dr. McTiernan fails to do so for all of the reasons set forth above and in Sections VI(A)(4)(a)(i) through (iii); her failure to adequately explain weighs strongly in favor of exclusion. Nonetheless, the Court has analyzed Dr.

McTiernan's expert opinion as best as it can, attempting to guess the grounds for her causation opinion, and the Court's analysis below is based upon its best understanding of Dr. McTiernan's methodology.

Third, as the Court noted in the preceding section, a case-specific application of a "flexible" Bradford Hill and weight-of-the-evidence approach is itself a methodology. The Court is permitted to consider the fact that Dr. McTiernan's ranitidine-specific methodology has not been employed by any published scientist or governmental body. The Court's authority to consider this fact is derived from the widespread acceptance factor as well as another core reliability factor in *Daubert*: whether the theory or technique has been subjected to peer review and publication. *Daubert*, 509 U.S. at 593. "[A] known technique which has been able to attract only minimal support within the community is likely to be found unreliable." *United States v. Downing*, 753 F.2d 1224, 1238 (3rd Cir. 1985). "[S]ubmission to the scrutiny of the scientific community is a component of 'good science,' in part because it increases the likelihood that substantive flaws in methodology will be detected." *Daubert*, 509 U.S. at 593.

Here, Dr. McTiernan has not published or otherwise sought peer review for the methodology that she employs to conclude that ranitidine causes cancer. Relatedly, no published scientist or governmental body has utilized Dr. McTiernan's methodology; to answer the question of whether ranitidine causes cancer, no published scientist or governmental entity has disregarded ranitidine active-comparator analyses in a study in favor of reliance upon non-user analyses in the very same study, has disregarded ranitidine epidemiology in favor of reliance upon dietary epidemiology, or has disregarded ranitidine epidemiology in favor of reliance upon occupational studies. To illustrate, the published, peer-reviewed scientists outside of this litigation did not rely

upon mailed dietary questionnaires to answer the ranitidine question. Nor did they rely upon a study premised upon people's preferences for barbeque.

And while the Court does not doubt that the various scientific authors *considered*[130] all available evidence on NDMA, including even animal studies, their respective opinions were *based* upon ranitidine epidemiology, ranitidine laboratory studies, ranitidine clinical trials, and comparisons between those who consume ranitidine and those who consume competing, similar medications. Stated another way, even the authors of the ranitidine studies that came the closest to finding evidence of an association between ranitidine and cancer did not rely upon dietary questionnaires to interpret their findings. Nor has any scientist outside of this litigation concluded that ranitidine epidemiology is unnecessary to answer the ranitidine question because dietary and occupational studies are sufficient. Dr. McTiernan is alone in her methodology.

To summarize, the fact that Dr. McTiernan conducts a Bradford Hill analysis as part of her final conclusion with a "weight-of-the-evidence" approach does not necessarily mean that, as applied, her methodology is conventional or generally accepted. Dr. McTiernan's methodology lacks not only widespread acceptance, but any acceptance in the scientific community. This lack of acceptance is evidence of an unreliable methodology, and this factor weighs strongly in favor of exclusion.

Fourth, the Court considers Dr. McTiernan's frequent reliance on statistically insignificant data. "[A]s many federal courts observe, if an expert places undue emphasis on statistically insignificant evidence, it may indicate that the expert's methods are unreliable." *In re Prempro*, 738 F. Supp. at 892. "[T]his court has frowned on causative conclusions bereft of statistically significant epidemiological support." *Wells v. SmithKline Beecham Corp.*, 601 F.3d 375, 380 (5th

[130] *See* DE 5915 at 34 (arguing that the scientific community, including the FDA, routinely considers dietary epidemiology).

Cir. 2010); *see also Joiner*, 522 U.S. at 145-47 (ruling that, where an expert opinion was founded on statistically insignificant data and other doubtful evidence, the district court did not abuse its discretion by excluding the opinion).

Here, far from being occasional or intermittent, Dr. McTiernan's reliance[131] on statistically insignificant results is routine; Dr. McTiernan relies upon statistically insignificant results in the following studies:

Yoon;
Kantor;
Adami;
Tran;
Iwagami;
Jakszyn;
Keszei;
Loh;
Rogers;
Zheng;
Larsson;
Pobel;
Song;
Rademacher; and
Knekt.[132]

Dr. McTiernan's frequent reliance upon statistically insignificant data stems from her belief that all data, regardless of the associated confidence intervals, may be relied upon in forming a causation opinion.

For all of the reasons set forth in Section VI(A)(4)(a)(iii), *supra*, and the Court's discussion of statistical significance in Section VI(A)(3)(b)(ii), *supra*, the Court concludes that Dr. McTiernan's high level of reliance upon statistically insignificant results is an "undue reliance"

[131] True, the Court cannot say with certainty just how much reliance Dr. McTiernan places upon the studies listed above. Based upon sheer volume, however, the Court concludes that Dr. McTiernan's reliance on statistically insignificant findings is high.

[132] This is not an exhaustive list of Dr. McTiernan's reliance upon statistically insignificant study results because the Court has made no effort to catalogue Dr. McTiernan's statistically insignificant citations to studies that did not examine ranitidine or NDMA, however, the Court deems this list sufficient to make its point.

that is indicative of an unreliable methodology. This factor weighs moderately in favor of exclusion.

Fifth, the Court concludes that Dr. McTiernan's methodology is unreliable because Dr. McTiernan has chosen to credit ranitidine epidemiology comparisons to non-users in specific studies to the exclusion of comparisons to the users of similar medications in the very same studies. *See In re Lipitor*, 892 F.3d at 634 ("Result-driven analysis, or cherry-picking, undermines principles of the scientific method and is a quintessential example of applying methodologies (valid or otherwise) in an unreliable fashion. Courts have consistently excluded expert testimony that cherry-picks relevant data because such an approach does not reflect scientific knowledge, is not derived by the scientific method, and is not good science." (internal quotation marks and citation omitted)). Dr. McTiernan's decision to disregard all active comparator analyses is contrary to every published scientist to have considered the matter, but when pressed to defend her opinion on the issue, Dr. McTiernan provided no legitimate justification and effectively abandoned any effort to cite to outside scientific support for her position. *See In re Zoloft*, 858 F.3d at 796 ("[I]f an expert applies certain techniques to a subset of the body of evidence and other techniques to another subset without explanation, this raises an inference of unreliable application of methodology.").

Thus, for all of the reasons the Court set forth in its discussion on this topic in Section VI(A)(3)(b)(i), *supra*, the Court concludes that Dr. McTiernan's selective disregard for data within a study that does not tend to support her conclusion (active comparisons), in conjunction with her emphasis on data within a study that better supports her conclusion (non-user comparisons), is indicative of a conclusion-oriented, unreliable methodology. It also calls into question the

reliability of Dr. McTiernan's criticisms of ranitidine studies that are unrelated to active comparator study design. This factor weighs strongly in favor of exclusion.

Sixth, there is a line of persuasive cases that stands for the proposition that, although epidemiological evidence is not required to prove causation, a plaintiff's expert must address epidemiological evidence that is inconsistent with his or her causation opinions. *See Norris*, 397 F.3d at 882 ("We are simply holding that where there is a large body of contrary epidemiological evidence, it is necessary to at least address it with evidence that is based on medically reliable and scientifically valid methodology."); *see also In re Zoloft (Sertralinehydrochloride) Prods. Liab. Litig.*, 176 F. Supp. 3d 483, 492-93 (E.D. Pa. 2016) ("[T]he Court holds that when epidemiological studies are equivocal or inconsistent with a causation opinion, experts asserting causation opinions must thoroughly analyze the strengths and weaknesses of the epidemiological research and explain why that body of research does not contradict or undermine their opinion."), *aff'd sub nom. In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787 (3d Cir. 2017); *Milward v. Rust-Oleum Corp.*, 820 F.3d 469, 475 (1st Cir. 2016) (affirming the exclusion of expert testimony where the expert failed to "explain why she disregarded other, incompatible research" and displayed a "complete unwillingness to engage with the conflicting studies"); *cf. Kuhn v. Wyeth, Inc.*, 686 F.3d 618, 633 (8th Cir. 2012) (permitting testimony despite the existence of epidemiological evidence that disfavored the expert's opinion where the expert relied on methodologically reliable epidemiological studies and provided an explanation for why those studies were chosen).

Similarly, several courts have held that district courts have discretion to exclude expert testimony where the expert's conclusions are anomalous compared to the conclusions of the other scientists in the field, and the expert has not provided reasons for the anomaly. *See Allison*, 184

F.3d at 1315 (holding that a district court did not abuse its discretion by excluding testimony based in part on four unreliable epidemiological studies that were "in direct contrast to over twenty other epidemiological studies"); s*ee also Lust By & Through Lust*, 89 F.3d at 598 ("[T]he district court can exclude the opinion if the expert fails to identify and defend the reasons that his conclusions are anomalous"); *Conde v. Velsicol Chem. Corp.*, 24 F.3d 809, 814 (6th Cir. 1994) (affirming the exclusion of expert testimony where the expert's conclusion was contrary to 19 epidemiological studies and where he did not "take issue with his peers and explain the grounds for his differences." (quoting *Turpin v. Merrell Dow Pharms., Inc.*, 959 F.2d 1349, 1360 (6th Cir. 1992))).

Here, there is no ranitidine epidemiology that concludes that ranitidine causes cancer. And, far from there being only a few or sporadic studies, there are many studies which found no statistically significant evidence of an association between ranitidine and cancer. Rather than explain why the various study authors were wrong in how they interpreted their own data, Dr. McTiernan and the Plaintiffs focus on what they see as weaknesses in the various ranitidine studies. What the Plaintiffs and Dr. McTiernan do not do, is "explain why that body of research does not contradict or undermine [her] opinion." Rather than engage with the *conclusions* of the ranitidine epidemiology authors and explain why her own causation opinion is not undermined by the field of ranitidine epidemiology, Dr. McTiernan comes close to silence on the conclusions of the study authors. Indeed, to find the conclusions of most of the various ranitidine studies, the Court had to read the studies for itself; most of the conclusions cannot be found in Dr. McTiernan's report or in the Plaintiffs' Response.[133]

[133] The Court additionally notes that the Plaintiffs' experts also omit the conclusions of dietary epidemiological study authors in their expert reports. As discussed in Section VI(A)(3)(b)(iii), *supra*, the vast majority of the dietary epidemiological study authors either concluded there was insufficient evidence of causation between cancer and NDMA or that the observed association was with the consumption of meat, not with NDMA.

Instead of fitting her own opinion into the larger field of ranitidine epidemiology,[134] Dr. McTiernan turns to the fields of occupational epidemiology on rubber factory workers and dietary epidemiology on the excessive consumption of meat. But far from explaining how her "anomalous" opinion is nonetheless based on "medically reliable and scientifically valid methodology," Dr. McTiernan relies on crude, unadjusted risk rates and statistically insignificant data from studies she criticizes, a study with four cancer patients, a study with five cancer patients, and studies attenuated from the ingestion of ranitidine. In summary, Dr. McTiernan's opinion is so far afield from the studies she relies upon, and her discussion of the conclusions of ranitidine study authors is so lacking (even for studies with data she uses), that the Court considers Dr. McTiernan's effective failure to reconcile her opinion with outside studies to be strongly indicative of an unreliable methodology, and a factor that weighs strongly in favor of exclusion.

Seventh, in the context of the general causation question in this MDL, Dr. McTiernan's reliance on dietary studies of meat consumption, and an occupational study on rubber factory workers in 1967, is not part of a reliable methodology. The analytical leap necessary for those studies is simply too great for all of the reasons set forth in the Court's discussion on this topic in Section VI(A)(3)(b)(iii), *supra*. Because of Dr. McTiernan's strong reliance upon these studies,[135] this factor weighs strongly in favor of exclusion.

Eighth, the Plaintiffs argue that their unique consumption of ranitidine either cannot be detected or was not detected in ranitidine epidemiology. *E.g.,* DE 5915 at 64 ("The issue here is

[134] At her deposition, Dr. McTiernan effectively evaded every effort by the Defendants to elicit testimony about whether ranitidine epidemiology, and only ranitidine epidemiology, was sufficient grounds for Dr. McTiernan's expert opinion. *E.g.*, McTiernan Dep. at 578-80 ("Q: Would it be possible for you to assess ranitidine [epidemiology] and determine whether it demonstrates an association [with cancer]? A: I don't know. I haven't done that. I looked at everything together.").

[135] The Court notes that while the specifics of Dr. McTiernan's reliance on the dietary and occupational studies is unknown, it may be inferred that her level of reliance was high given the trend of ranitidine epidemiology to undermine her general causation opinion and the number of pages Dr. McTiernan devoted to dietary and occupational studies.

not the terminology of 'long-term' or 'short-term' use, but whether the exposure duration in the studies matches the exposure duration for Plaintiffs in this case. It does not."). In pressing this argument, the Plaintiffs fail to meet their "indispensable" burden to show evidence of a dose-response relationship. *Chapman*, 766 F.3d at 1308. Some ranitidine studies attempted to observe evidence of a dose-response relationship between high levels of ranitidine consumption and cancer, but no study concluded such a relationship existed, with some even observing the inverse of a dose-response relationship. As for the ranitidine dosage that produces a response, Dr. McTiernan has no opinion:

> Q. Are you going to offer an opinion about a minimum dose and duration of exposure to ranitidine that is necessary to cause stomach cancer?
>
> A. Today, at this point, I don't have an opinion on that.
>
> Q. Okay. And is that answer also true for the other four cancers that you're opining on?
>
> A. Yes.
>
> . . . .
>
> Q. Okay. You mentioned the 47 nanograms, I think. How long does somebody need to be exposed to 47 nanograms of NDMA daily to cause stomach cancer?
>
> . . . .
>
> A. So in short, from the epidemiologic data, I don't have an opinion on how long somebody needs to have an intake of 47 nanograms of NDMA to cause cancer.

McTiernan Dep. at 607-08.

On the topic of frequency, if the Plaintiffs' frequency of consumption of ranitidine placed them into a rare, high-risk category of ranitidine users, such that their rate of cancer cannot be detected amongst the masses of less-frequent ranitidine users, the Court notes that this theory of the case has not been pled. The Plaintiffs have not pled a narrowed, nuanced case where, due to incredibly high and unusual ranitidine consumption, the Plaintiffs—through that high level of

consumption—developed cancer. Instead, the Plaintiffs' pled theory of the case is that every part of the ranitidine supply chain—manufacturer, distributor, and retailer—may be held liable for any and all amounts of ranitidine consumption, no matter how small.[136] Indeed, the Plaintiffs' experts have gone so far at the *Daubert* stage as to argue that there is no safe dosage—none—of any amount of NDMA and through it, ranitidine. *See infra* Section VI(B). For the Plaintiffs to argue there is no safe amount of ranitidine consumption, but to also simultaneously argue that their idiosyncratic use of ranitidine simply cannot be detected in ranitidine epidemiology, means that the Plaintiffs have no reliable evidence of a dose-response relationship.

For all of the reasons set forth in Section VI(B), *infra*, the Plaintiffs have failed to produce reliable evidence of a dose-response relationship outside of the field of epidemiology. Dr. McTiernan has also failed to do so within the field of epidemiology. This factor weighs in favor of exclusion.

Ninth, in addition to taking inconsistent positions on the topic of dose-response relationship, the Plaintiffs and their experts take inconsistent positions in their criticisms of ranitidine epidemiology. The Plaintiffs' Response repeatedly emphasizes that the follow-up period in ranitidine epidemiology was too short to detect a relationship between ranitidine use and cancer, which is in turn based upon their retained experts' opinions: "Plaintiffs' experts evaluated each [ranitidine] study, and 'none of the studies had adequate follow-up time to capture the full latency period of cancer development, but several of the studies had such short follow-up times that they were virtually guaranteed not to detect an increased risk of cancer with ranitidine use.'"

[136] At the motion to dismiss stage, the Plaintiffs relied upon the allegation that, had the Defendants taken some action—such as alter ranitidine's expiration dates—the Plaintiffs would not "have consumed the volume of NDMA that they ultimately did and would not have been harmed from the NDMA." DE 3683 at 24. This allegation meant that the Plaintiffs' NDMA consumption from ranitidine, no matter how small and no matter which Defendant was responsible, was what caused the Plaintiffs' harm. *Id.*

DE 5915 at 66. The median follow-up time in the various ranitidine studies ranged from as low as 2.4 years to as high as 14 years, with a median follow-up time in Nørgaard of 11-14 years, Nørgaard et al., *supra*, at 8, and in Adami of 12-14 years, Adami et al., *supra*, at 19. Yet the Plaintiffs' experts based their opinions on dietary epidemiology with follow-up times comparable to, or even less than, ranitidine epidemiology.

Both Dr. McTiernan and Dr. Moorman base their opinions on the Jakszyn and Keszei dietary studies, with Dr. Moorman assigning "moderate" weight to both studies and "little" weight to almost every ranitidine study. Dr. Moorman also relies upon a third dietary study on processed meat, Vingeliene.[137] Jakszyn had a median follow-up time of 8.7 years. Jakszyn et al., *supra*, at 555. The Keszei follow-up time was 16.3 years. Keszei et al., *supra*, at 136. The Vingeliene follow-up times ranged from 10 to 16 years. Moorman Report at 182. The Plaintiffs and their experts do not adequately explain why the follow-up times in Jakszyn, Keszei, and Vingeliene were sufficient to detect an association with cancer, but the follow-up times in ranitidine studies were not.

Relatedly, the Plaintiffs and the Plaintiffs' experts' opinions on follow-up times stand in contrast to the characteristics of the Plaintiffs themselves. Pursuant to the Plaintiffs' Response, 40% of the thousands of Plaintiffs in this MDL consumed ranitidine for less than 10 years and now allege that they have cancer caused by ranitidine. DE 5915 at 18. As for the necessary follow-up time for exposure to result in cancer, pursuant to the registered data of over 50,000 claimants in this MDL who intend to file a ranitidine case, the vast majority of the ranitidine users began to consume ranitidine within the past 15 years. If most ranitidine users with cancer in this MDL started to consume ranitidine less than 15 years ago, and if 40% of those users took ranitidine for

[137] The Court does not discuss Vingeliene in this Order because it was a study on processed meat that did not estimate NDMA intake.

less than 10 years, it appears to this Court that it is inconsistent for the Plaintiffs to argue (and their experts to opine) that a dose-response relationship cannot be detected via ranitidine epidemiology, which had follow-up times as high as 11-14 years. Indeed, the Plaintiffs have gone so far as to opine that as little as three years of ranitidine consumption can result in a detectable increase of cancer risk. *Compare* DE 5915 at 95 ("The longest dose-response measurement was three years (Cardwell) and that study did demonstrate a dose-response relationship as reported by the authors."), *with id.* at 98 ("Dr. McTiernan specifically discusses the dose-response found in the Cardwell study. . . . This is extraordinary evidence for dose-response, since 3 years is a short period.").

At a minimum, it falls upon the Plaintiffs and their experts to provide a reasoned explanation for this inconsistency. This they have not done. Dr. McTiernan's inconsistent positions on dose-response relationship are part of a broader trend described throughout this Order; each of Dr. McTiernan's departures from science outside of this litigation (such as the disregard of active comparators, the disregard of statistical significance, the disregard of conclusions, and high levels of reliance on attenuated studies to answer the causation question in this MDL) follows the same trend because each such departure favors the same outcome—finding general causation. The Court may consider this trend (and it does) as evidence of result-driven reasoning, a factor in favor of exclusion. *In re Mirena II*, 341 F. Supp. 3d at 251 ("[When e]ach of [an expert's] departures from settled and rigorous methodology favors the same outcome," it raises "a red flag" that "suggests motivated, result-driven reasoning."); *In re Zoloft*, 858 F.3d at 796.

Tenth and finally, even if the Court is wrong as to some subset of the Court's prior nine conclusions, each of which weigh in favor of exclusion, the Court's ruling is on Dr. McTiernan's methodology in the totality. Weighing all factors and evidence in the totality, the Court concludes

that, pursuant to *Daubert*, Dr. McTiernan's methodology is unreliable. The Defendants' Epidemiology Motion is granted as to Dr. McTiernan.

b. **Dr. Moorman**

Dr. Moorman is the Plaintiffs' second of two retained epidemiologists. Dr. Moorman's official opinion is that "ranitidine causes cancer in humans, and specifically it causes bladder, liver, pancreatic, esophageal, and stomach cancer." Moorman Report at 6. In addition to bringing the same arguments against Dr. Moorman that the Defendants brought against Dr. McTiernan, the Defendants make a Moorman-specific argument that her opinion is outcome-driven and is not the result of a reliable, scientific, objective methodology. In response, the Plaintiffs argue that Dr. Moorman's opinion is not outcome-based and is the result of a reliable methodology.

Many of the grounds that the Court articulated for the exclusion of Dr. McTiernan apply to Dr. Moorman, and the Court will set forth those grounds again below, in Section VI(A)(4)(b)(iii). There is one key difference, however, between Dr. McTiernan and Dr. Moorman. While the Court had to guess at how various studies impacted Dr. McTiernan's analysis, Dr. Moorman's methodology is more transparent; Dr. Moorman clearly explains what studies most influence her opinion, and she explains why those studies influence her opinion.[138] As a result, the Court does not question the reliability of Dr. Moorman's expert opinion because she fails to adequately explain her methodology.

Dr. Moorman uses a Bradford Hill analysis and a weight-of-the-evidence approach to render her expert opinion. The Court: (i) examines the justifications Dr. Moorman gives for choosing the studies most important to her ultimate conclusion, and the Court also (ii) examines

[138] One other difference between Dr. McTiernan and Dr. Moorman is that, in the Court's opinion, Dr. Moorman relied upon statistically insignificant data with less frequency than Dr. McTiernan.

the specific studies that are most important to Dr. Moorman before finally (iii) reaching its ultimate conclusion.

i. Grounds for Selecting Persuasive Studies

Dr. Moorman ranks four ranitidine studies as strongly impacting her ultimate conclusion: Liu, Tran, Cardwell, and McDowell. Each study is drawn from the same medical database, the Primary Care Clinical Informatic Unit, a database in Scotland. Dr. Moorman assigns "little" weight to every other ranitidine study.

Dr. Moorman assigns a "strong" weight to the Tran study because of its sample size and because of the length of time the database covered. *See* Moorman Report at 65. Dr. Moorman assigns the same weight to the Liu, Cardwell, and McDowell studies for identical reasons. *Id.* at 64-65, 87, 198. Dr. Moorman also assigns "strong" weight to her selected studies because of "good ascertainment of exposure." Moorman Dep. at 103. Because Dr. Moorman assigns "strong" weight to four studies from the same database, and because Dr. Moorman utilizes the same justification for her reliance for each study, the Court discusses in greater detail the Primary Care Clinical Informatic Unit database and the Court also discusses the three different justifications Dr. Moorman gives for her assignment of "strong" weight.

<u>Primary Care Clinical Informatic Unit Database Studies and the Length of Databases</u>

Each of the Primary Care Clinical Informatic Unit database studies was a nested case-control study. A nested case-control study is where a case-control study is conducted within a defined cohort. Moorman Report at 10. The defined cohort in the database studies were those who developed a Designated Cancer. From within the cohort, the authors divided subjects into cases (those who took ranitidine and developed cancer) and controls (those who took ranitidine and did not develop cancer). A primary study-design challenge in a case-control study or a nested-case

control study is selecting appropriate controls to compare to the cases who developed cancer. Important to the Court's analysis below, what is *not* a challenge in a case-control or a nested case-control study, is how long study participants must be "followed" by researchers. When a nested case-control study is conducted, the researchers already know who developed cancer and who did not. There is no need to "follow" study participants to see if cancer develops. Instead, the need to follow study participants is a challenge inherent in cohort-style studies.

In a cohort study, a group of individuals are identified who were exposed to an agent of interest, ranitidine. Those participants are then followed by researchers over time to see who develops cancer and who does not. If follow-up is too short, cancer cases that may have developed in the future (had follow-up been longer) are not observed. Most of the ranitidine epidemiological studies in this MDL are cohort studies, and Dr. Moorman criticizes the follow-up time in the cohort studies as being too short.

This criticism appears on page 59 of the Plaintiffs' Response, where the Plaintiffs argue that the follow-up time in the ranitidine epidemiology cohort studies was too short to detect an association between ranitidine and cancer. The relevant excerpt reads as follows:

> So, how many human ranitidine studies have a follow-up period of about 30 years? None. 20 years? None. Plaintiffs' experts evaluated each study, and "[n]one of the studies had adequate follow-up time to capture the full latency period of cancer development, but several of the studies had such short follow-up times that they were virtually guaranteed not to detect an increased risk of cancer with ranitidine use." The study authors were candid about this limitation.

DE 5915 at 66 (emphasis omitted). Immediately following this discussion, the Plaintiffs paste a chart showing the follow-up time in the various ranitidine studies. The numerical data on the chart reads as follows:

Study	Follow-Up
Yoon	7 years (maximum)
Kantor	6.7 years (median)
Iwagami	2.4 years (median)
Kumar	4.4 years (median)
Adami	12-14 years
Nørgaard	11-14 years (median)
Kim Y.D.	10 years (maximum) Below 5 years (median)
Kim S.	5 years
Habel	8-13 years
Tran	5.6 (median)
Cardwell	Similar to 18 years
McDowell	Same as Cardwell

Id. at 66-67. The top of the Plaintiffs' chart lists the follow-up times for the various ranitidine cohort studies for which Dr. Moorman assigns "little" weight. Three of the four studies that Dr. Moorman assigns "strong" weight to are at the bottom of the chart: Tran, Cardwell, and McDowell. The Court makes three observations about the chart.

First, the Plaintiffs have omitted the Liu study from the chart, even though Dr. Moorman assigns strong weight to that study. Second, the Plaintiffs' chart attempts to make an improper comparison by classifying Cardwell and McDowell as having "similar to 18 years" of follow-up time. The Plaintiffs' reference to 18 years is accompanied by a footnote which reads: "Cardwell was a nested case-control study, for which the concept of 'median follow-up' is not the same as a

cohort study. But the length of the study conveys analogous information." *Id.* at 67 n.177. The Court agrees with the Plaintiffs' footnote that a case-control study such as Cardwell does not include the concept of a "median follow-up" time. For that reason, it is inappropriate to imply that studies such as Cardwell have follow-up times and therefore may be compared to the follow-up times in the cohort-style studies at the top of the chart. The Court believes that the Plaintiffs attempt to make such a comparison so as to bolster their position that the Cardwell and McDowell studies should be credited in lieu of the other studies at the top of the chart, consistent with Dr. Moorman's opinion.

Third, it is the length of the Cardwell and McDowell databases (referenced in the Plaintiffs' footnote) that causes Dr. Moorman to credit those studies over other studies. To quote Dr. Moorman's report, she found those studies persuasive because of "[their] use of a database to ascertain drug use over a period of up to 18 years." Moorman Report at 87. This figure stems from the length of the prescription database records, which spanned 18 years, in the Primary Care Clinical Informatic Unit studies. Cardwell et al., *supra*, at 2. Because Dr. Moorman chooses to assign "strong" weight to Cardwell, McDowell, Tran, and Liu because of the length of the time in the prescription database records, the Court would expect, at least all else being equal, for all other ranitidine studies to have shorter database records. To make such a comparison, the Court recreates below the Plaintiffs' chart, using the length of time of database records as the metric for comparison:

Study	Length of Database
Yoon	8 years
Kantor	9 years
Iwagami	13 years
Kumar	20 years
Adami	22 years
Nørgaard	22 years
Kim Y	9 years
Kim S	11 years
Habel	8-13 years
Tran	12 years
Liu	12-14 years
Cardwell	18 years
McDowell	18 years

The Court observes that the length of time in the Liu (12-14 years), Tran (12 years), Cardwell (18 years), and McDowell (18 years) databases was comparable to, and in some cases less than, the Iwagami (13 years), Kumar (20 years), Adami (22 years), and Nørgaard (22 years) databases.[139]

[139] Many metrics may be used to compare the volume of information in the various databases such as median exposure time, median follow-up time, total patients studied, total ranitidine patients studied, and the number of cancer outcomes amongst ranitidine users. Although the Court chose two metrics for discussion (number of years and number of ranitidine users who developed cancer), the Court could have utilized other metrics to demonstrate its point—that Dr. Moorman's databases of choice are not particularly different in terms of scope or size as compared to many of the ranitidine studies that Dr. Moorman did not find persuasive.

Primary Care Clinical Informatic Unit Database Studies and Sample Size

Dr. Moorman also weighs her selected four studies as "strong" because of the studies' "large sample size." *E.g.,* Moorman Report at 198. The Court would therefore expect, as a general matter, for Dr. Moorman's four studies to have larger sample sizes than the other ranitidine studies. Re-using the formatting of the Plaintiffs' chart, the Court sets forth below various sample sizes:

Study[140]	**Sample Size of Ranitidine Users that Developed Cancer**
Yoon	400 (liver), 118 (bladder), 450 (stomach)
Kantor	13 (liver), 16 (bladder)
Iwagami	263 (stomach)[141]
Kumar	367 (stomach)
Adami	342 (stomach), 517 (pancreatic), 276 (esophageal), 133 (liver)
Nørgaard	270 (bladder)
Kim S	306 (stomach)
Kim Y	880 (liver), 170 (stomach), 320 (pancreatic), 180 (esophageal)
Habel	7 (bladder/kidney), 6 (stomach / esophageal) 5 (pancreatic)
Tran	45 (liver)
Liu	128 (stomach)
Cardwell	455 (bladder)
McDowell	143 (pancreatic)

[140] The study and cancer pairings in this chart are the Court's best effort to summarize the sample sizes referenced in Dr. Moorman's report. The Court's summary of the data on its two charts above matches the Plaintiffs' summary of the data. *See* Defendants' Sept. 21 *Daubert* Hearing Tr. at 260.
[141] The Iwagami study commingled ranitidine users with nizatidine users.

For ranitidine users who developed cancer, the Court observes that the Primary Care Clinical Informatic Unit studies either had smaller sample sizes than other ranitidine studies (Tran, Liu, and McDowell) or had roughly comparable sample sizes (Cardwell).

Turning from the Plaintiffs' chart to Dr. Moorman's deposition, Dr. Moorman was asked to define what constitutes an appropriate sample size, but Dr. Moorman declined to provide precise clarification on this issue:

> Q. In your opinion, what is an appropriate sample size to evaluate the relationship between ranitidine use and any of the five cancers in this case? . . . .
>
> A. Once again, you know, there is a continuum of sample sizes, and there are many considerations that it depends on. So, you know, just to give one example, having a very large cohort that you didn't follow for very long, that might not be an informative study just because you're not seeing the—an adequate number of cancers to detect the relative risk. It's—I cannot give an exact number for what is an adequate sample size. It depends on the study design and, you know, other characteristics as well.

Moorman Dep. at 103-04. Because of Dr. Moorman's answer—an appropriate sample size must be determined based upon a study design—Dr. Moorman was asked which studies in this MDL had a large sample size:

> Q. Out of the ranitidine observational studies that you reviewed in this case, what did you consider to be a larger sample size? . . . .
>
> A. You know, again, it is a continuum, and again, it can—it's—the sample size is somewhat based on study designs. Cohort studies will have larger sample sizes in general as compared to case-control studies. I could not give, like, any particular threshold of this is an adequate sample size and inadequate. It all depends on the individual studies.

Id. at 104. After further questions on this topic, Dr. Moorman described the Cardwell study as having a large, adequate sample size. *Id.* at 105. Dr. Moorman contrasted Cardwell with the Nørgaard study which, as described by Dr. Moorman, "had many fewer cases than the Cardwell study." *Id.* Later, Dr. Moorman conceded that the Cardwell study had 455 ranitidine cancer cases,

and that Nørgaard had 270. *Id.* at 110, 112. The Court observes that, as compared to the 270 cases in Nørgaard that Dr. Moorman deemed insufficient, there were 128 cases in Liu and 143 cases in McDowell, both of which Dr. Moorman deems sufficiently great to warrant "strong" weight.

Good Ascertainment of Exposure

Dr. Moorman also assigns "strong" weight to her four selected studies because of a good "ascertainment of exposure." *Id.* at 103. But the Court notes that Nørgaard, a study with a comparable sample size, a large database, a (in Dr. Moorman's own words) large follow-up period, and which Dr. Moorman describes as having "high quality data for cancer outcomes and prescription drugs," receives "little" weight in Dr. Moorman's final analysis. Moorman Report at 72. The Nørgaard study authors found no association between ranitidine and invasive bladder cancers. Nørgaard et al., *supra*, at 10.

In Section VI(A)(3)(b)(iii), *supra*, the Court addressed at length how, consistent with the Plaintiffs' experts' own testimony, the ascertainment of exposure in dietary studies is an inherent, known, and challenging problem in the field of dietary epidemiology. Distilled down, it is difficult to estimate exposure to an agent based upon a dietary questionnaire, which is in turn based upon one's memory. Given the inherent problems in dietary epidemiology with ascertainment of exposure and given Dr. Moorman's heavy reliance on ascertainment of exposure to select persuasive studies, the Court would expect, all else being equal, for Dr. Moorman not to assign "strong" weight to a dietary study. And she does not. What Dr. Moorman does do, however, is assign a "moderate" weight to four dietary studies (and one occupational study) while simultaneously assigning "little" weight to most ranitidine studies.

One such dietary study that Dr. Moorman assigns a "moderate" weight to is Ronco, which estimated NDMA exposure in Uruguayan men using dietary questionnaires. Moorman Report at

100. Ronco did not quantify the amount of NDMA exposure in the various tertiles of exposure and had a moderate (for this MDL) sample size of 255 cancer cases. *Id.* Ronco therefore at least facially stands in contrast to the Nørgaard ranitidine study discussed above which, unlike Ronco, receives "minimal" consideration from Dr. Moorman. Much like Nørgaard, the Adami study had a comparable sample size, high quality data on prescription drug use (according to Dr. Moorman), and a "relatively" long follow-up period (also according to Dr. Moorman). The Adami authors found: "that our study provides little evidence that ranitidine, whether through NDMA contamination or any other reason, increases risk of upper gastrointestinal cancers." Adami et al., *supra*, at 14. In contrast to the Adami study, though, to which Dr. Moorman assigns "little" weight, Ronco, a study using a dietary questionnaire to estimate exposure, receives "moderate" weight. Moorman Report at 123.

ii. Studies Assigned "Strong" Weight

Liu. The Liu study focused on stomach cancer, but the purpose and design of the study were not to estimate the risks of ranitidine use. *See* Peipei Liu et al., *Use of Proton Pump Inhibitors and Histamine-2 Receptor Antagonists and Risk of Gastric Cancer in Two Population-Based Studies*, 123 Brit. J. Cancer 307, 307 (2020); *see also* Moorman Report at 66 ("Dose-response analyses were conducted for all PPIs and all H2-blockers but not specifically for ranitidine. There were no analyses that directly compared ranitidine users to users of other acid-suppressing drugs."); McTiernan Report at 145 ("[Liu's] primary focus was to look at associations between use of proton pump inhibitors or H2 blockers in general and risk for stomach cancer."). Accordingly, the study authors expressed no conclusion on ranitidine. Indeed, the word "ranitidine" only appears in the text of the study on two occasions. Because ranitidine was not the focus of the study, the study contained no data on a dose-response relationship for ranitidine.

To control for the possibility that a ranitidine user started taking ranitidine because of cancer symptoms (known as reverse causation), the Liu authors removed from the data pool a cancer diagnosis that was within one year of the initial use of ranitidine. Liu et al., *supra*, at 314. Based upon that one year of lag-time, and based upon 128 ranitidine users who developed cancer, the study authors computed a statistically significant relative risk rate for ranitidine use, as compared to non-use, of 1.42 (confidence interval 1.1 to 1.85). *Id.* at 312. When the authors used a lag time of two years, however, the resulting risk rate dropped to a statistically insignificant 1.22 (confidence interval .89 to 1.67). *Id*. When the lag time was increased to three years, the rate dropped further to 1.17 (confidence interval .81 to 1.68). *Id.*

This same pattern—greater lag time reducing the observed association—was seen in the drug actually being studied in Liu—cimetidine—and when H2-blockers and PPIs were combined and analyzed together. *See id.* For example, when all H2-blockers were analyzed together, the combined risk rate with one year of lag-time was 3.07, but when 4-5 years of lag time was added, the risk rate dropped to a statistically insignificant 1.29. *Id.* In their own words, the study authors summarized their findings as follows:

> In both the PCCIU case–control and UK Biobank cohort studies, we observed little consistent evidence of an increased risk of gastric cancer with PPI use. Although using a 1-year lag there was an association between PPI and gastric cancer, this association did not follow an exposure response (for instance, those using for the shortest period had the highest risk) and was attenuated with longer lags **suggesting the role of reverse causation** (for instance, associations weakened when prescriptions in the 2-year period prior to diagnosis were removed in the PCCIU, and incident gastric cancers within 2 years after baseline were removed in the UK Biobank). A similar pattern of association was observed in PCCIU for H2RA, but there was no association between H2RA use and gastric cancer in the UK Biobank.
>
> . . . .
>
> To conclude, we found some evidence of the associations between PPI and H2RA use and gastric cancer risk in a large population-based case–control and a cohort study. These associations were sensitive to the duration of lag time used in the

> analysis. **Our results revealed a marked increase in the prescription of acid suppression medications immediately before gastric cancer diagnosis suggesting the role of reverse causation.**

Id. at 313-14 (emphasis added). With the Liu study author's conclusions in hand, the Court quotes below Dr. Moorman's discussion of Liu in her expert report:

> Liu, *et al*. [55] reported on both a nested case-control study and a cohort analysis conducted in the UK. The nested case-control study was conducted using the Primary Care Clinical Information Unit Research database. Each of the 1119 cases of gastric cancer within the cohort was matched with up to 5 controls (n=5393) within the same database. Exposure was based on prescription data from 1996 through 2011. Information was also available on important confounders such as age, sex, smoking status and comorbid conditions. The OR for gastric cancer associated with ever use of ranitidine was 1.42, 95% CI 1.10-1.85. For any PPI use, the OR was 1.49, 95% CI 1.24-1.80 and for any H2RA use the OR was 1.44, 95% CI 1.16-1.80). Analyses of both H2RAs and PPIs showed that associations were stronger for use closer to the time of diagnosis.
>
> This study [sic] strengths include its large sample size and its use of a database to ascertain drug use over a period of up to 18 years. Its limitations include the fact that the electronic database had no prescription data prior to 1996, which could have resulted in misclassification of exposure if some former users of ranitidine were not captured in their database. In addition, the database did not capture non-prescription use of ranitidine, which again could have resulted in the misclassification of some ranitidine users as non-users, although it has been estimated that over-the-counter purchases account for only ~10% of ranitidine sold in the UK,[113] To the extent that ranitidine users were misclassified as non-users, the result would be an underestimate of the true relative risk. Overall, this was a well-designed and conducted study with many strengths and relatively few weaknesses. I weighted this study strongly in my analysis.

Moorman Report at 198. Dr. Moorman's analysis of Liu therefore omits the conclusion of the study authors, and it makes no mention of the authors' belief that they had found evidence "suggesting the role of reverse causation." The closest Dr. Moorman comes to acknowledging the author's findings on reverse causation is her statement that: "Analyses of both H2RAs and PPIs showed that associations were stronger for use closer to the time of diagnosis." *Id.* Dr. Moorman cites to the highest relative risk associated with ranitidine that may be found in the study—1.42—

but she omits any mention of the fact that additional analyses of ranitidine (using longer lag times) resulted in lower, statistically insignificant risk rates.[142]

Tran. The Tran study was completed before the FDA's initiation of a voluntary recall of ranitidine. Perhaps because of its earlier inception, the Tran study's primary focus was on PPIs, not H2-blockers. Due to the study's non-ranitidine focus, no dose-response relationship information for ranitidine appears in the study. Additionally, the Tran study only compared ranitidine users to non-users; it did not include an active comparator analysis. Tran et al., *supra*, at 55. The Tran study used two different databases. *Id.* One database was the Primary Care Clinical Informatics Unit, the same database used in Cardwell. *Id.* The other database was the UK Biobank, the same database used in Kantor. *Id.* As to the Primary Care database, the study authors computed a relative risk rate of 1.41 with a confidence interval of .91 to 2.15. *Id.* at 60. Using the UK Biobank database, the study authors computed, based upon 8 cases that developed liver cancer, a relative risk rate of 1.82, with a confidence interval of .87 to 3.79. *Id.* at 61. Based upon these statistically insignificant results, the study authors concluded: "[T]here was little evidence of association with use of H2-blockers." *Id.* at 50. The study author's conclusion is not referenced in Dr. Moorman's discussion of the study. *See* Moorman Report at 65.

Cardwell. Using the Primary Care Clinical Informatics Unit Research database, researchers studied a possible link between 455 ranitidine users and bladder cancer. Publishing their results in May of 2021, the authors facially found an association between ranitidine use and bladder cancer when comparing ranitidine users to non-users. The authors also facially found an association with bladder cancer when ranitidine use was compared to users of PPIs. When comparing ranitidine users to other H2-blocker users, however, researchers found "little evidence

[142] In another section of her report, Dr. Moorman references the data, but not the authors' conclusions, on reverse causation and lag times. Moorman Report at 65-66.

of [any] difference in bladder cancer risk." Cardwell at al., *supra*, at 6. Notwithstanding a facial association between ranitidine and bladder cancer (as compared to non-users of ranitidine and PPI users), the researchers did not conclude ranitidine caused cancer in part because, *inter alia*, "smoking and alcohol [data] were incomplete . . . and consequently, there remains the possibility of residual confounding." *Id.* at 7. In lieu of any conclusion on causation, researchers recommended further studies "in an attempt to replicate [their] findings." *Id.* at 1.

McDowell. Published in January of 2021, researchers used the same database as the Cardwell study—the Primary Care database in Scotland. Unlike Cardwell, however, this study focused on pancreatic cancer. Researchers found a positive association between ranitidine use and pancreatic cancer when ranitidine users were compared to non-users: showing a risk rate of 1.37 with a corresponding confidence interval of 1.1 to 1.7. McDowell et al., *supra*, at 3. Even so, researchers were not prepared to conclude that ranitidine was associated with pancreatic cancer for at least two reasons. First, "there was no definitive exposure-response relationships" between ranitidine and pancreatic cancer because the adjusted risk rate for those who took the most ranitidine was less (and was not statistically significant) than those who took the least amount of ranitidine. *Id.* at 1. Second, the researchers did not undertake an active comparator analysis between ranitidine users and the users of competing drugs, and the authors noted that other studies that did conduct such a comparison actually found a decreased risk of developing pancreatic cancer if one consumed ranitidine. In light of the above, the McDowell authors noted: "[T]he association between ranitidine and pancreatic cancer is yet to be determined." *Id.* at 7.

iii. Final Ruling as to Admissibility of Dr. Moorman's Testimony

Below, delineated in **bold**, the Court explains nine reasons why, as a case-specific, fact-specific matter, it deems Dr. Moorman's methodology to be unreliable. When applicable, the

Court discusses the *Daubert* standard and explains how its case-specific conclusions fit within the framework of *Daubert* case law.

First, the Court agrees with the Defendants that Dr. Moorman utilizes a results-based, conclusion-oriented process to select the studies for "strong" and "moderate" weight in her analysis. For a Bradford Hill analysis or a weight-of-the-evidence approach to be reliable, "there must be a scientific method of weighting that is used and explained." *In re Zoloft*, 858 F.3d at 795. Thus, weights must be assigned to data according to a scientific approach. *Id.* at 796 ("[T]he assessment or weighing of that evidence must not be arbitrary, but must itself be based upon methods of science." (quoting *Magistrini*, 180 F. Supp. 2d at 602)). Otherwise, the expert may engage in a "conclusion-oriented selection process." *Id.* A conclusion-oriented process is a "malleable and vague approach" that is "in tension with first principles under *Daubert*, because it makes it all too easy for an expert to manipulate the Bradford Hill factors to support a desired conclusion of causation, and far too hard for an ensuing expert to replicate and rigorously test the expert's analytic approach." *Id.*

To be sure, it is ordinarily a role for an expert—not a court—to select how much weight a study should or should not be afforded. But "where experts have claimed to apply Bradford Hill, courts have insisted on a clear explication of the weighting assigned to the different criteria. They have also demanded that the expert's application of the individual criteria be performed with proper rigor." *Mirena II*, 341 F. Supp. 3d at 247-48. "[T]he specific techniques by which the weight of the evidence/Bradford Hill methodology is conducted must themselves be reliable according to the principles articulated in *Daubert*." *In re Zoloft*, 858 F.3d at 796; *see id*. ("An expert can theoretically assign the most weight to only a few factors, or draw conclusions about one factor based on a particular combination of evidence. The specific way an expert conducts

such an analysis must be reliable; 'all of the relevant evidence must be gathered, and the assessment or weighing of that evidence must not be arbitrary, but must itself be based on methods of science.'" (quoting *Magistrini*, 180 F. Supp. 2d at 602)).

Here, the Court believes that Dr. Moorman does not select the data inputs for her Bradford Hill analysis and reach her ultimate conclusion based upon objective, scientific criteria for several reasons. First, Dr. Moorman's stated reasons—such as the length of time in databases, sample sizes, and good ascertainment of exposure—are inconsistently applied across ranitidine and dietary studies. By way of example, the Court does not believe that Dr. Moorman's criteria, applied objectively, could result in a dietary study of Uruguayan men's consumption of meat (Ronco) being assigned greater weight than almost all of the available epidemiology on ranitidine.

Second, Dr. Moorman omits and all but ignores the study authors' conclusions in the studies she relies upon, the majority of which contradict her opinion and, at the very least, do not support her opinion. Third, Dr. Moorman selects data from studies that fit with her ultimate opinion while simultaneously ignoring data in the very same studies that do not fit with her opinions. For example, Dr. Moorman relies upon non-user comparisons in the Cardwell study while disregarding Cardwell comparisons to H2-blockers; the Cardwell H2-blocker comparator data does not even appear in Dr. Moorman's expert report.

Fourth and finally, Dr. Moorman's opinions and criticisms are internally inconsistent. For example, Dr. Moorman relies upon the Cardwell study, and finds that it had evidence of a dose-response relationship, but the Cardwell data referenced by Dr. Moorman had an exposure period ranging from 3 to 8.4 years. Moorman Report at 111; Cardwell et al., *supra*, at 4, 6. Thus, even though Dr. Moorman opines that as little as three years of exposure (or perhaps 8.4 years of median exposure) is sufficient to observe a dose-response relationship, she does not adequately

acknowledge the possibility that the Nørgaard and Adami studies, with 14 years of follow-up, may have, consistent with her opinions, adequate follow-up time to observe an association. *Compare* Moorman Report at 31 ("Additional limitations of the ranitidine studies that used an active comparator design including [sic] inadequate follow-up periods."), *with id.* at 70-71 (characterizing Adami and Nørgaard follow-up time as "long," but assigning "little" weight to the studies).

To be sure, an expert such as Dr. Moorman may choose to assign less weight to studies such as Nørgaard and Adami for reasons unrelated to those studies' follow-up time. But it falls to this Court to decide, based upon the totality of Dr. Moorman's expert report and deposition, whether Dr. Moorman selects the inputs into her Bradford Hill analysis based upon an objective, scientific-based criteria, or if she instead selects her inputs based upon a results-oriented, conclusion-driven methodology. Reviewing Dr. Moorman's expert opinion in its totality, the Court concludes that Dr. Moorman utilizes a conclusion-oriented process to select the inputs (to assign weights to the various studies) into her Bradford Hill analysis. This factor weighs strongly in favor of exclusion.

Second, although the primary focus of a *Daubert* inquiry is an expert's *methodology*, this Court is permitted to consider the fact that the Plaintiffs' experts' general causation *conclusions* on ranitidine, including Dr. Moorman's conclusion, are unique and isolated to this litigation—no independent scientist or publication has concluded that ranitidine causes cancer. Dr. Moorman's opinion is excluded on this ground for the same reasons set forth in Section VI(A)(4)(a)(iv), *supra*, the Court's ruling on widespread acceptance and Dr. McTiernan. This factor weighs moderately in favor of exclusion.

Third, a case-specific application of a "flexible" Bradford Hill and weight-of-the-evidence approach is itself a methodology. The Court is permitted to consider the fact that Dr. Moorman's ranitidine-specific methodology has not been employed by any published scientist or governmental body. Dr. Moorman's opinion is excluded on this ground for the same reasons set forth in Section VI(A)(4)(a)(iv), *supra*, the Court's ruling on Dr. McTiernan. This factor weighs strongly in favor of exclusion.

Fourth, the Court concludes that Dr. Moorman's methodology is unreliable because, without a valid scientific basis, Dr. Moorman chooses to credit ranitidine epidemiology comparisons to non-users in specific studies to the exclusion of comparisons to the users of similar medications in the very same studies. Dr. Moorman's opinion is excluded on this ground for the same reasons set forth in Section VI(A)(4)(a)(iv), *supra*, the Court's ruling on Dr. McTiernan. This factor weighs strongly in favor of exclusion.

Fifth, there is a line of persuasive cases that stand for the proposition that, although epidemiologic evidence is not required to prove causation, a plaintiff's expert must address epidemiologic evidence that is inconsistent with his or her causation opinions. Dr. Moorman's opinion is excluded on this ground for the same reasons set forth in Section VI(A)(4)(a)(iv), *supra*, the Court's ruling on Dr. McTiernan. This factor weighs strongly in favor of exclusion.

Sixth, in the context of the general causation question in this MDL, Dr. Moorman's reliance on dietary studies of processed meat, and an occupational study on rubber factory workers in 1967, is not part of a reliable methodology. Dr. Moorman's opinion is excluded on this ground for the same reasons set forth in Section VI(A)(4)(a)(iv), *supra*, the Court's ruling on Dr. McTiernan. This factor weighs strongly in favor of exclusion.

Seventh, the Plaintiffs argue that their unique consumption of ranitidine either cannot be detected or was not detected in ranitidine epidemiology, and this argument is sourced in Dr. Moorman's opinions. Dr. Moorman's opinion is excluded on this ground for the same reasons set forth in Section VI(A)(4)(a)(iv), *supra*, the Court's ruling on Dr. McTiernan. This factor weighs in favor of exclusion.

Eighth, in addition to taking inconsistent positions on the topic of dose-response relationship, the Plaintiffs take inconsistent positions in their criticisms of ranitidine epidemiology. Dr. Moorman's opinion is excluded on this ground for the same reasons set forth in Section VI(A)(4)(a)(iv), *supra*, the Court's ruling on Dr. McTiernan. This factor weighs in favor of exclusion.

Ninth and finally, even if the Court is wrong as to some subset of the Court's prior eight conclusions, the Court's analysis of Dr. Moorman's methodology is in the totality. Viewed in the totality, the Court concludes that, pursuant to *Daubert*, Dr. Moorman's methodology is unreliable and the Defendants' Epidemiology Motion is granted as to Dr. Moorman.

c. **Plaintiffs' Experts' Supplemental Reports on Newly-Published Wang Study**

After the parties completed their *Daubert* briefing and the Court held oral argument on the Defendants' *Daubert* Motions, the Plaintiffs filed an expedited motion to supplement the expert opinions of five of their experts: Drs. Le, McTiernan, Michaels, Moorman, and Salmon. DE 6041. The basis for the Plaintiffs' motion was a ranitidine-based epidemiological study that had been published a few days before the motion to supplement was filed, the Wang study. Chun-Hsiang Wang et al., *Pharmacoepidemiological Research on N-nitrosodimethylamine-Contaminated Ranitidine Use and Long-Term Cancer Risk: A Population-Based Longitudinal Cohort Study*, 19 Int'l J. Env't Rsch. & Pub. Health 1, 1 (2022). The Court granted the Plaintiffs' motion to

supplement; the parties filed supplemental expert reports, conducted depositions of the five experts, and filed supplemental briefing in conjunction with their experts' supplemental reports. *See* DE 6056.

The Size and Scope of the Wang Study

The Wang study is a cohort study using the Taiwan Health Insurance Research Database. Wang et al., *supra*, at 1. Like most other ranitidine-based epidemiological studies in this MDL, the Wang study actively compared ranitidine users to the users of a competing H2-blocker (famotidine). *Id.* In terms of the size of its database, the Wang study included 181 ranitidine users who developed bladder cancer, 121 who developed pancreatic cancer, 255 who developed stomach cancer, 101 who developed esophageal cancer, and 711 who developed liver cancer. *Id.* at 8. With the exception of liver cancer (which was high), the number of ranitidine users who developed cancer in Wang was similar to other ranitidine studies. In terms of the length of the Wang database, the median follow-up time in Wang was 8.42 years, putting the Wang study in the middle of all ranitidine studies in terms of follow-up time. *Id.* at 3.

The Results of the Wang Study

Comparing ranitidine users to non-users, the Wang study authors found a statistically significant risk rate of 1.22 for liver cancer (with a confidence interval ranging from 1.09 to 1.36), 1.26 for stomach cancer (ranging from 1.05 to 1.52), and 1.35 for pancreatic cancer (ranging from 1.03 to 1.77). *Id.* at 6. For the remaining Designated Cancers in this MDL, bladder and esophageal, the results were not statistically significant. *See id.* The risk rate was 1.27 for esophageal cancer (ranging from .95 to 1.70) and 1.06 for bladder cancer (ranging from .86 to 1.30). *Id.* at 7.

When the study authors actively compared ranitidine users to famotidine users, however, the risk rates for stomach cancer and pancreatic cancer ceased to be statistically significant. *Id.* at

10. The active-comparator risk rates for bladder cancer and esophageal cancer were not statistically significant as well. *Id.* The active comparator analysis for liver cancer, however, did result in a statistically significant risk rate of 1.22 (ranging from 1.06 to 1.40). *Id.*

The Conclusions of the Wang Study Authors

As a threshold matter, the Wang study authors surveyed the available data on ranitidine and NDMA, including the ranitidine epidemiological studies discussed above in Section VI(A)(3) and studies on animals. *Id.* at 2. Based upon that review, the opinion of the Wang study authors was: "The conflicting results of studies underlie the lack of concrete evidence supporting the role of ranitidine in cancer development." *Id.* Based on their own data, for two of the Designated Cancers in this MDL, bladder and esophageal, the study authors described their findings as "no significant association[]." *Id.* at 6. For the remaining Designated Cancers—liver, stomach, and pancreatic—the study authors probed further and looked for evidence of a dose-response relationship.[143]

For pancreatic cancer, the study authors' estimated risk rate for those who took the most amount of ranitidine (1.22) was statistically insignificant and was less than the estimated risk for those who took the least amount of ranitidine (1.64). *Id.* at 9. For stomach cancer, the estimated risk rate for those who took the most amount of ranitidine (1.33) was barely statistically significant and was almost the same as those who took the least amount of ranitidine (1.26). *Id.* For liver cancer, the results were more defined. Those who took the most amount of ranitidine had a statistically significant risk rate of 1.42, and those who took the least amount of ranitidine had a risk rate of 1.03. *Id.* Based upon that data, the study authors addressed only liver cancer as follows:

> [B]ased upon a direct comparison with either the non-ranitidine group or the famotidine group (similar indication to ranitidine users), **only liver cancer** displayed a significant association with long-term ranitidine use.

[143] Dose-response relationship data for bladder cancer and esophageal cancer does not appear in the Wang study.

Id. at 12 (emphasis added). The final conclusion of the study authors, appearing at the end of their publication, reads as follows:

> To conclude, the clinically meaningful results of this large-scale, longitudinal population-based cohort study using an excellent prescription and cancer database provide concrete evidence with very convincing long-term follow-up information for exploring the causative role of ranitidine in increasing the risk of carcinogenic effects on the liver, which was primarily caused by increasingly heavier ranitidine usage. However, to elucidate the underlying mechanisms of its causal association, further studies are necessary.

Id. at 13.

i. Parties' Arguments

The Defendants argue that Wang is an unreliable study because the active comparator design employed by the study authors has a fundamental flaw that artificially increases the relative risk of ranitidine use. The Defendants further argue that the Plaintiffs' experts' attempt to include Wang as part of the evidentiary support for their expert opinions highlights and demonstrates that the experts utilize a conclusion-oriented methodology to produce their opinions. In response, the Plaintiffs argue that the Wang study design was reliable and that their experts appropriately relied upon Wang as additional evidentiary support for their expert opinions.

ii. Analysis

Some of the Defendants' arguments go to whether the Wang study reliably analyzed its data. Perhaps, as the Defendants argue, the Wang study design caused the liver cancer risk estimate to be too high. Perhaps, as the Plaintiffs argue, the Wang study design was reliable and appropriate. The resolution of this dispute is not the focus of the Court's *Daubert* analysis. What the Court does focus on is *how* the Plaintiffs' experts have attempted to incorporate the Wang study into their pre-existing general causation opinions. In the Court's opinion, this falls within a topic that the Defendants labeled "situational science" at oral argument.

At oral argument, the Defendants described situational science as follows: "Simply put, Dr. McTiernan applies whatever method is expedient to get to her desired conclusion. That is the antithesis of reliable science . . . ." Defendants' Sept. 21 *Daubert* Hearing Tr. at 132. Situational science was a concept addressed in *Caraker v. Sandoz Pharmaceuticals Corp.*, 172 F. Supp. 2d 1046 (S.D. Ill. 2001). When the district court in that case described an expert's use of epidemiological evidence, it noted that the expert "attack[ed] the epidemiological studies as fundamentally flawed, while, at the same time, selectively pluck[ing] favorable numbers (that [were] not statistically significant) and herald[ing] them as crucial pieces of" his expert opinion. *Id.* at 1049. Situational science was also discussed in the *Lipitor* MDL. *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Pracs. & Prods. Liab. Litig.*, 892 F.3d 624 (4th Cir. 2018). In *Lipitor*, an expert performed a test which did not result in a statistically significant result. *Id.* at 634. The expert then performed another test, with different parameters, and the second test got a statistically significant result. *Id.* The expert's report showed the results from the second test but omitted the first test. *Id.* The district court took no issue with the first test or the second test per se, but the omission of the first, statistically insignificant result called into question the reliability of the expert's methodology. *Id.* at 634-35. The circuit court agreed, noting that the expert's methodology "lacked the hallmark of science properly performed." *Id.* at 635.

The two characteristics of situational science discussed above are present in the Plaintiffs' experts' opinions in this case, which the Court described in Sections VI(A)(3) and (4), *supra*. Essentially, the Plaintiffs' experts "pluck data" and omit data and conclusions from studies that run contrary to the experts' opinions. The Plaintiffs' experts do not agree with any ranitidine study author's conclusion, and, instead, the Plaintiffs' experts extract data from studies, even when the data is statistically insignificant, and "herald" the data as important to the general causation

question. By way of example, Dr. Moorman relies upon the Liu study, yet the Liu study authors concluded that they had found evidence in their data of reverse causation. Liu et al., *supra*, at 313. The Liu authors' conclusions on reverse causation were omitted from Dr. Moorman's analysis. Similarly, Dr. Moorman relies upon non-user data from Cardwell while omitting (and disregarding) the active-comparator Cardwell data. As yet another example, Dr. McTiernan relies upon crude, unadjusted data taken from supplementary tables appended to a study publication in lieu of the adjusted data forming the basis for the authors' conclusions. *See supra* Section VI(A)(4)(a)(i).

Assuming that the Defendants are correct about the Plaintiffs' experts' proclivity to engage in situational science, then, upon the publication of the Wang study, the Court would expect two things to occur. First, the Court would expect that the Plaintiffs' experts continue to selectively extract data from Wang that supports their causation opinion, while omitting that which is contrary to the experts' causation opinions. Second, the Court would expect that the Plaintiffs' experts' criticisms of the other ranitidine studies, to the extent that they apply to the Wang study as well, would either be omitted from the expert's discussion of Wang or would no longer be deemed important. Upon inspection, both expectations came to fruition. Each is addressed in turn.

<u>Selective Extraction and Omissions</u>

Neither Dr. Moorman nor Dr. McTiernan, the Plaintiffs' two primary epidemiologists, acknowledge the conclusions of the Wang study authors in their supplemental expert reports. Neither expert acknowledges the threshold conclusion in Wang that the available data on ranitidine (upon which, the Plaintiffs' experts previously concluded that there was sufficient evidence of general causation) equated to a "lack of concrete evidence" of ranitidine's ability to cause cancer. Neither expert acknowledges the Wang study's characterization of the data on esophageal and

bladder cancer (that there was "no significant association" between ranitidine and those cancers). Neither expert acknowledges the conclusion in Wang that "only liver cancer" had sufficient long-term evidence of association. Finally, neither expert acknowledges that the Wang study's final, ultimate conclusion: that although there was "clinically meaningful" data in support of the proposition that ranitidine can cause liver cancer, "further studies are necessary" to reach the conclusion that ranitidine does, in fact, cause liver cancer.

To locate and analyze these conclusions, the Court had to independently review the Wang study. The Court therefore concludes that Drs. McTiernan and Moorman omit key information about the Wang study from their expert reports, and that the omissions are uniformly contrary to the experts' opinions.

Additionally, the Court does not believe that the final conclusions of the Wang study authors mirror the Plaintiffs' general causation expert opinions; the Wang authors stopped short of concluding that ranitidine causes liver cancer. Alternatively, even if the Wang study could be interpreted as concluding ranitidine causes liver cancer, there certainly exists (as the Court concluded in Section VI(A)(4)(a)(i), *supra*) no widespread acceptance of the Plaintiffs' experts' general causation opinions, even post-Wang, within the scientific community.[144] And the Wang authors undoubtedly reached no final, causal conclusion on any cancer other than liver cancer.

Relatedly, the Wang study authors did not employ the Plaintiffs' experts' methodology. They did not consider dietary studies or occupational studies to be sufficient to answer the general causation question, of greater importance than ranitidine-based studies, or of equal importance to ranitidine-based studies, nor did the authors utilize those sorts of studies to any degree of significance to formulate a causation opinion. The Wang authors merely reference dietary,

[144] There is no consensus amongst the liver cancer ranitidine studies as described in Section VI(A)(4)(a)(i), *supra*.

occupational, and animal-based studies to support a mechanistic theory and explain why their human-based ranitidine study was a worthwhile endeavor. *See* Wang et al., *supra*, at 11.

Although the Wang study made no ultimate conclusion on any cancer other than liver cancer, Dr. McTiernan concludes that Wang further supports her opinion for *all* of the Designated Cancers. McTiernan Supplemental Report at 9-10. Similarly, Dr. Moorman concludes that the Wang study supports her conclusions for all of the Designated Cancers. DE 6041 Ex. C at 6 (addressing liver, esophageal, stomach, and pancreatic cancers); Moorman Supplemental Dep. Tr. at 542-43 (contending that the Wang study data supports an association with bladder cancer). In reaching their opinions, the Plaintiffs' experts again premise their analysis on much statistically insignificant data, even when their opinions run contrary to the Wang authors' characterizations of the very same data, and even while omitting any discussion of how the Wang authors analyzed their own data.

Criticism Inconsistencies

Active Comparators. As discussed at length in Section VI(A)(3)(b)(i), *supra*, the Plaintiffs' experts previously took the position that all active comparators analyses in ranitidine epidemiology were fundamentally flawed. Those analyses were flawed, according to the Plaintiffs' experts, because every H2-blocker and every PPI increases cancer risk, just like ranitidine. Additionally, Dr. McTiernan described her disfavor of ranitidine epidemiology active comparator analyses as follows: "The problem is that with the ranitidine studies being compared to other similar drugs, H2 blockers or proton pump inhibitor drugs, what I've seen in these studies is that those populations look very different." McTiernan Dep. at 686; *see also id.* at 121 (specifically criticizing the usefulness of famotidine as an active comparator). As summarized by the Court in Section VI(A)(4)(a), *supra*, Dr. McTiernan did not rely upon active comparator analyses as part

of her final analysis, and, for the most part, Dr. McTiernan neither acknowledged nor discussed active comparator data in the text of her expert report, instead citing non-user comparison data and even crude, unadjusted data. Indeed, when analyzing studies with active comparator data, Dr. McTiernan chose to rely upon other data points. Before Wang, there was no statistically significant active comparator association between ranitidine and a Designated Cancer that Dr. McTiernan could rely upon.

Once Wang was published, there *was* a statistically significant active comparator association that Dr. McTiernan could rely upon. And she does, finding the active comparator analyses in Wang are a part of the study's strengths. McTiernan Supplemental Report at 4 ("[T]o address the issue of indication bias, the researchers also did comparisons to famotidine users and to PPI users. That elevated risks for several cancers were found for all three analyses strongly support the validity of the study findings."). Instead of omitting the active comparator study results from her supplemental expert opinion, as she did in her original opinion, Dr. McTiernan both cites and discusses the results. Dr. McTiernan does not disregard the active comparator analyses because of the potential of famotine to cause cancer, nor does she credit the potential of the famotidine population to "look very different" from the ranitidine population as a study weakness. When listing the various strengths of the Wang study, Dr. McTiernan reports, "[T]hey examined associations between ranitidine use and specific cancer risk comparing ranitidine users to active comparators—the H2 blocker—famotidine, and PPIs. Given these *improved* methodologies in the Wang et al. study, it strengthened my causal analyses." *Id.* at 9 (emphasis added).

Concerning Dr. Moorman, she omits active comparator results from her table of data in her original expert report, even when the results were generated in Cardwell, a study that she strongly

relies upon. Moorman Supplemental Dep. at 579-82.[145] In addition to criticizing ranitidine active comparator study designs because of the potential of other drugs to cause cancer, Dr. Moorman previously had the following to say:

> The complexities of interpreting the active comparator studies **given the multiple mechanisms by which ranitidine and other acid-suppressing drugs could cause liver cancer** (as well as the additional complexities introduced by study limitations such as exposure misclassification), make it difficult, **if not impossible**, to make a determination of the overall risk for liver cancer from use of ranitidine in these studies.

Moorman Report at 152 (emphasis added); *see also id.* at 28, 31 (specifically criticizing the usefulness of famotidine as an active comparator).[146] Upon Wang's publication, far from concluding that the Wang active comparator data was "difficult, if not impossible" to consider because of the "multiple mechanisms by which ranitidine and other acid-suppressing drugs could cause liver cancer," Dr. Moorman concludes that the Wang active comparator analysis is a study **strength**. DE 6041 Ex. C at 4.

Propensity Scoring. Propensity scoring is a system where researchers attempt to control for confounding by creating a comorbidity "score" for a study participant; the more confounding comorbidities a participant has, the higher his or her score and, through the score, the researchers estimate the propensity of the subject to contribute to confounding. *See* McTiernan Supplemental Dep. at 48-53. The Adami study used a propensity score, but because the underlying data used to create the score was not published in the study, Dr. McTiernan criticized the Adami study's use of a propensity score. *See* McTiernan Rebuttal Report at 15. In the context of a discussion on ranitidine epidemiology's "serious limitations," Dr. McTiernan went so far as to state: "Propensity

[145] At her deposition, Dr. Moorman maintained, without citation, that she referenced the Cardwell active comparator data in the text of her expert report, even if she did not reference the data in the tables of her expert report. The Court has searched the text of Dr. Moorman's expert report and was unable to locate the active comparator data from Cardwell.

[146] In their discussion on this topic on page 19 of their supplemental brief, the Plaintiffs omit the earlier bolded portion of Dr. Moorman's earlier expert opinion.

scoring does not make up for missing variables." *Id.* According to Dr. McTiernan, the propensity score system in Adami, which removed 75% of potential cases, resulted in "too small a number of cases to have the power to detect statistically significant associations." *Id.*

The Wang study also used propensity scoring, and the study authors removed a sizeable percentage[147] of potential cases because of their propensity scores. Wang et al., *supra*, at 4, 5. Yet Dr. McTiernan does not consider Wang's usage of a propensity score to be a negative or even neutral aspect of the study; instead, Dr. McTiernan classifies the Wang study's use of a propensity scoring system as a strength in her analysis. McTiernan Supplemental Report at 8. Additionally, with the exception of liver cancer, the number of cancer cases in Wang was smaller—not larger—than the number of cancer cases in Adami.

Liver and Metastatic Cancer. Dr. McTiernan previously criticized the Adami study on an additional ground. Although the Adami study identified liver cancer patients using a nationwide cancer registry, Dr. McTiernan notes that the liver cancer cases could have been misidentified because cancer developed in some other area of the body and then metastasized into the liver. McTiernan Report at 226-27. Dr. McTiernan's concern was that the liver cases in Adami could therefore have been counted too high. *See id.* The Wang study, like Adami, utilized a national cancer registry database, but Dr. McTiernan's supplemental report does not raise any concerns about metastasized cancer or a miscounting of liver cancer cases in Wang.

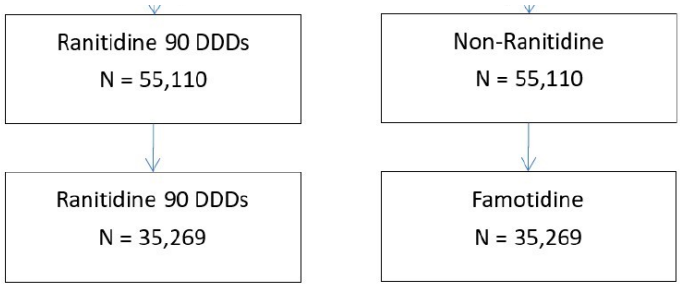
Applying International Studies to Plaintiffs in the United States. As part of her pre-Wang expert opinion, Dr. McTiernan criticizes the Defendants' experts for their reliance upon five ranitidine-based, active comparator epidemiological studies because those studies were conducted outside of the United States. McTiernan Rebuttal Report at 31. The basis for Dr. McTiernan's

[147] The Court cannot ascertain the precise impact of propensity scoring on potential cases in the Wang study from the text of the study.

criticism was that the Defendants' experts should have explained how the "prescribing practices[] and patient adherence to medications" in other countries could be applied to the Plaintiffs in the United States. *Id.* Although the Wang study was conducted with the population of Taiwan, there is no part of Dr. McTiernan's supplemental report that explains how the prescribing practices or patient adherence to medications in Taiwan may be applied to the Plaintiffs in the United States.

The Reliability of the Wang Active Comparator Analysis

In addition to the arguments outlined above, the Defendants also contend that the active comparator analysis in Wang was conducted unreliably in a manner different from all other ranitidine epidemiology. From the text and data of the study, there is a substantial inference that the study authors chose to compare those who took the *most* of ranitidine (greater than 90 daily doses) to *everyone* who took famotidine, as exemplified in the following table describing the design of the study:



Wang et al., *supra*, at 5. In other words, the study authors may have compared those who needed acid suppression medication the most to those who needed acid suppression medication the least. The Defendants questioned Dr. Moorman at her deposition over whether such a comparison could reliably ascertain the risk of ranitidine use:

> Q. If the Wang study did in fact compare longer-term users of ranitidine to all users of famotidine, would that raise any concerns for you?
>
> A. Again, this study does not give information about dose on ranitidine—I'm sorry. It doesn't give any information about dose of famotidine use. So we just don't

> know. The dose of the famotidine could be less than in the ranitidine group. It could be more. We just—it's just not reported in there.

Moorman Dep. at 602. Because Dr. Moorman did not answer the posed question, the Defendants asked the question again:

> Q. Again, I'd like you to focus on my question. If, in fact, these authors were comparing higher doses or longer-term users of ranitidine to all users of famotidine, would that raise any concerns for you? . . . .
>
> A. Again, we don't know what is going on here. It would certainly depend on the level—you know, the comparison of the doses between the ranitidine group and the famotidine group. . . .

Id. at 602-03. The Court makes two observations about this exchange. First, Dr. Moorman takes the position that one simply cannot tell from the text of the Wang study just precisely how the Wang active comparator analysis was designed. Second, depending upon how the design was structured ("it would depend upon the level"), Dr. Moorman's opinion on the Wang study could change.

Neither Dr. Moorman nor the other Plaintiffs' experts appear to have had the time to contact the Wang authors and carefully consider these matters.[148] Dr. Moorman first learned about the Wang study's publication on October 1, 2022. *Id.* at 528. She submitted her supplemental report on October 3. *Id.* at 529.

Upon review of the Wang study, the experts' supplemental reports, and the experts' deposition, the Court is concerned that the Plaintiffs' experts did not seek additional information on the study design, that the Plaintiffs' experts rendered opinions without that information, and that the Wang study may contain errors in describing how the study was conducted. As these are

[148] The Wang study raises other questions about its study design. For example, it is unclear from the text of the study whether the pool of ranitidine users had, at any point, also taken famotidine. Wang et al., *supra*, at 6.

not the only matters before the Court, however, the Court makes no determination on the reliability of the Wang study and instead bases its decision on other grounds.

Conclusion

The Plaintiffs' experts could conclude that the active comparator analysis in Wang was "difficult, if not impossible" to use, just like the active comparator analyses in prior ranitidine studies. Instead, the Plaintiffs' experts rely upon the active comparator analysis in Wang, which was the first such analysis to be statistically significant and favor their conclusions, while simultaneously disregarding the active comparator analyses in other studies that were statistically insignificant and were less favorable to their expert opinions. *See Soldo v. Sandoz Pharms.*, 244 F. Supp. 2d 434, 557, 560 (W.D. Pa. 2003) ("[I]nconsistency is the hallmark of a decidedly unscientific approach."). The Plaintiffs' experts also omit the conclusions of the Wang authors from their expert opinions and omit the Wang authors' analysis of their own data. *See In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d at 1362 ("Because the [study authors] themselves do not conclude that there is a causal relationship . . . it is inappropriate for Plaintiffs' experts to draw that conclusion for them.").

Taken as a whole and viewing the record in its totality, the Court agrees with the Defendants that Drs. McTiernan and Moorman engage in situational science and that their supplemental reports lack "the hallmark of science properly performed." For all of the reasons set forth in the Defendants' Supplemental Briefing,[149] the Court concludes that the Plaintiffs' experts' supplemental opinions are, like their original opinions, unreliable. The Court's prior rulings in this Order remain undisturbed and unaltered by the Supplemental Reports. Indeed, the Supplemental Reports underscore and reaffirm the Court's prior rulings.

[149] The Court adopts and incorporates herein the arguments the Defendants made in their "Brand Defendants' Supplemental Brief Regarding Wang Study" that are not inconsistent with this Order. DE 6099.

At this point in the Court's analysis of the epidemiology, the Court has only addressed Drs. McTiernan and Moorman with specificity. The Court now turns to Drs. Salmon, Michaels, and Le, and explains why its detailed analysis was confined to the opinions of Drs. McTiernan and Moorman.

d. **Drs. Salmon, Michaels, and Le**

The Plaintiffs have retained three experts who are not epidemiologists but nonetheless opine on epidemiology. The first, Dr. Salmon, is a toxicologist.[150] The second, Dr. Michaels, is a pathologist. The third, Dr. Le, is a pharmacist. Putting aside whether a toxicologist, a pathologist, and a pharmacist are qualified to give opinions on epidemiology,[151] these three experts' opinions and methodologies parallel the opinions of the Plaintiffs' two epidemiologists, Drs. McTiernan and Moorman. Briefly stated, the three non-epidemiologists disregard active comparator data in favor of comparisons to non-users, greatly rely upon dietary studies, greatly rely upon the occupational study on rubber factory workers, rely upon statistically insignificant data, lack widespread acceptance for their opinions and methodologies in the scientific community outside of this litigation, and do not seek peer review for any of their opinions in this litigation. In short, there is no meaningful difference between the opinions and methodologies of the Plaintiffs' non-epidemiologists who render epidemiological opinions and the Plaintiffs' epidemiologists.

At oral argument, the Plaintiffs conceded that, should Dr. Moorman and Dr. McTiernan be excluded for the broad, "overarching arguments" set forth in the Defendants' Epidemiology Motion, Drs. Salmon, Michaels, and Le's opinions on epidemiology would be due for exclusion as well. Defendants' Sept. 22 *Daubert* Hearing Tr. at 27. As the Court will grant the Defendants'

[150] The Court's analyzes Dr. Salmon's dose-response relationship opinions in detail in Section VI(B), *infra*.
[151] Because the Plaintiffs' experts are stricken on other grounds, the Court need not determine whether the three non-epidemiologist experts are qualified to render opinions on epidemiology.

Epidemiology Motion in full as to Drs. McTiernan and Moorman, including for the broader, "overarching" arguments set forth by the Defendants, the Court excludes the epidemiological opinions of Dr. Salmon, Dr. Michaels, and Dr. Le for all of the reasons set forth in Sections VI(A)(4)(a)(iv) and (b)(iii), *supra*.

e. **Dr. Hidajat**

Dr. Hidajat was retained by the Plaintiffs as a rebuttal expert in this case. In an abundance of caution, the Defendants have moved to exclude Dr. Hidajat as a primary, case-in-chief general causation expert. In response, the Plaintiffs concede that Dr. Hidajat was not retained to provide a general causation opinion. DE 5915 at 51. Accordingly, the Court grants the Defendants' Epidemiology Motion as to Dr. Hidajat as a general causation expert and denies the Defendants' related motion to strike Dr. Hidajat [DE 5460] on procedural grounds as moot.

5. Final Ruling on Epidemiology Motion

For all of the reasons set forth in this Order, including its ruling on secondary evidence, *see supra* Section V; *infra* Section VII, the Brand Defendants' Motion to Exclude Plaintiffs' General Causation Experts' Opinions Related to Epidemiology [DE 5699] is granted. In closing its discussion on epidemiology, however, the Court thinks that a demonstrative is helpful. The Plaintiffs' expert Dr. Salmon testified at his deposition that, of all the epidemiological studies in this MDL, the most "influential" study is the Cardwell study. Salmon Supplemental Dep. at 18. In his own words: "I think that the contributions of the other studies are important but not as influential." *Id.* at 20. Other Plaintiffs' experts, such as Dr. Moorman, make Cardwell a centerpiece of their causation opinions as well.

After the Plaintiffs' experts finalized their supplemental expert reports, a journalist in the United Kingdom interviewed Dr. Cardwell. Salmon Supplemental Dep. Ex. 5. The subject of the interview was Dr. Cardwell's ranitidine study findings. From the interview:

> Professor Chris Cardwell, a public health statistician at Queen's University Belfast, who led the study, told Good Health that while the finding is interesting, it should be treated with caution until further studies are performed into the possible association.
>
> It could perhaps be a statistical quirk, he says.
>
> "Alternatively, it could be that the ranitidine users were different from non-ranitidine users in ways that we could not adjust for, such as family history or occupational exposures," he adds.

Id. at 4. Dr. Cardwell's statement in the article that further studies should be performed is consistent with the conclusion in the text of his study, although that conclusion was omitted in the Plaintiffs' experts reports. Of note to the Court is that Dr. Cardwell expressed caution about the interpretation of his findings in light of the potential for confounding that underpins the chronic use of ranitidine. Juxtaposed to the need for caution expressed by Dr. Cardwell, the Plaintiffs' experts make the Cardwell study a centerpiece of their epidemiological opinions. Although the Court concludes (without relying on the article) that the Plaintiffs' experts' opinions and methodologies lack widespread acceptance in the scientific community, the Court believes that this interview by Dr. Cardwell further underscores the point. At the end of the day, the Plaintiffs' experts make analytical leaps that no scientist outside of this litigation has made. And the leaps go too far.

B. Dose-Response Relationship

The Court has previously focused on one type of primary evidence, epidemiology. The Court's analysis on that topic was lengthy because it was the sole focus of one of the Defendants' three *Daubert* Motions. It was also the subject of a considerable amount of oral argument. The

Court now turns to the second type of evidence recognized by the Eleventh Circuit as "primary" evidence, a dose-response relationship.

Unlike epidemiology, the topic of dose-response relationship received minimal discussion in the parties' briefing and only a moderate amount of discussion in the expert reports. Indeed, on one topic related to dose-response relationship—threshold dose—the Court did not even know the Plaintiffs' position until the Court pressed the Plaintiffs for such a position at oral argument. *E.g.,* Defendants' Sept. 21 *Daubert* Hearing Tr. at 21-22. Upon questioning, the Plaintiffs relied upon Dr. Salmon for a discussion of threshold dose and dose-response. Of all of the Plaintiffs' experts offering opinions on dose-response relationship and threshold dose, Dr. Salmon's opinion is the most extensive. Accordingly, the Court addresses Dr. Salmon's opinions on dose-response relationship and threshold dose at length below. Because the Plaintiffs' remaining experts spend only a minimal amount of time on dose-response relationship and threshold dose, the Court devotes a smaller amount of discussion to the remaining experts.

For background, "[t]he relationship between dose and response is 'the hallmark of basic toxicology' and the 'single most important factor to consider' in evaluating the toxicity of a drug." *In re Abilify*, 299 F. Supp. 3d at 1307 (first quoting *McClain*, 401 F.3d at 1242-43; then quoting *Chapman*, 766 F.3d at 1307). Dose-response relationship describes how changes in the amount, intensity, or duration of exposure to an agent affects the risk of disease, either by increasing or decreasing that risk. *See supra* Section VI; *see also In re Abilify*, 299 F. Supp. 3d at 1307. For example, where a substance exhibits a positive dose-response relationship, an increase in how much or how long a person is exposed to the substance would increase that person's risk of developing the disease in question. The general causation "expert who avoids or neglects [dose-response relationship] without justification casts suspicion on the reliability of his methodology,"

McClain, 401 F.3d at 1242, though the expert is not required "to give precise numbers about a dose-response relationship," *Williams v. Mosaic Fertilizer*, LLC, 889 F.3d 1239, 1248 (11th Cir. 2018) (quoting McClain, 401 F.3d at 1241, 1241 n.6).

A concept that is related to, yet distinct from dose-response relationship,[152] is "threshold dose." Threshold dose is the minimum amount of a substance below which the substance would not cause the disease or effect, even where exposure occurs repeatedly over the long-term. *Id.* (citing David L. Eaton, *Scientific Judgement and Toxic Torts—A Primer in Toxicology for Judges and Lawyers*, 12 J. L. & Pol'y 1, 16 (2003)). Threshold dose is an extremely important concept in toxic torts because, on the one hand, chronic low-dose exposures may be completely detoxified by the body and never cause any damage, whereas on the other hand, *any* substance in high enough amounts has the potential to be toxic. *In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d at 1351-52. A reliable general causation opinion must provide a threshold dose at which the substance becomes harmful. *McClain*, 401 F.3d at 1241 (holding that opinions claiming that "any level [of a particular substance] is too much" are insufficient to show threshold dose).

Four of the Plaintiffs' experts—Drs. McTiernan, Moorman, Panigrahy, and Salmon—opine that the NDMA in ranitidine exhibits a positive dose-response relationship. The Plaintiffs bear the burden to show that their experts' dose-response relationship and threshold dose opinions are reliable evidence of general causation for each of the five Designated Cancers. *See Frazier*, 387 F.3d at 1260. The Defendants argue that none of the Plaintiffs' experts have provided admissible opinions regarding either dose-response relationship or threshold dose. Defendants'

[152] Another concept that is related to dose-response relationship is "specific dose." Specific dose describes the actual exposure, including amount and duration, that an individual plaintiff had to a substance. Courts have, at times, referred to both threshold dose and specific dose as simply "dose," however, it is important to distinguish between these two concepts: threshold dose is a general causation inquiry which establishes "the levels of exposure that are hazardous to human beings generally," *McClain*, 401 F.3d at 1241 (quoting *Wright*, 91 F.3d at 1106), whereas specific dose is a specific causation inquiry that establishes a plaintiff's actual level of exposure. To carry her burden and recover in a toxic tort case, a plaintiff must establish that her specific exposure was at least as high as the threshold exposure. *Id.*

Sept. 22 *Daubert* Hearing Tr. at 215; *see also* DE 5699 at 94, 97-98; DE 5696 at 24-35; DE 5958 at 8.

In the following sections, the Court addresses the Plaintiffs' experts' opinions on dose-response relationship and threshold dose. First, the Court addresses the expert opinions of Dr. Salmon because he provides the Plaintiffs' most comprehensive dose-response relationship and threshold dose opinions. The Court then turns to the other Plaintiffs' experts' opinions on dose-response relationship and threshold dose.

1. Dr. Salmon's Dose-Response Relationship and Threshold Dose Opinions

Dr. Salmon primarily bases his dose-response relationship opinion on his review of the scientific literature, and he bases his threshold dose opinion on his own analyses.

a. **Summary of Evidence**

First, for dose-response relationship, Dr. Salmon opines that animal studies, discussed at length in Section VII(A), *infra*, provide clear evidence of a linear dose-response relationship at low doses of NDMA. The occupational and dietary epidemiological studies also provide evidence of a linear dose-response relationship at real-life exposure levels of NDMA. Salmon Report at 132-33. Further, Dr. Salmon opines that Cardwell demonstrated a positive dose-response relationship for bladder cancer, as evidenced by a statistically significant increased risk of bladder cancer after only three years of ranitidine exposure. *Id.* at 144. In his supplemental report on the Wang study, Dr. Salmon opines that Wang demonstrated a dose-response relationship for liver and gastric cancer. Salmon Supplemental Report at 4.

Next, for his threshold dose opinion, Dr. Salmon provides two threshold dose analyses: (1) lifetime cumulative exposure analysis and (2) years of exposure analysis. First, the lifetime cumulative exposure analysis estimates the amount of time one would have to consume ranitidine

to reach a measurable, "increased risk of cancers demonstrated in the NDMA dietary and occupational exposure studies." Defendants' Sept. 21 *Daubert* Hearing Tr. at 78. The dietary and occupational studies are central to Dr. Salmon's calculations because he uses those studies to estimate the total amount of NDMA the subjects consumed over the course of their lifetimes. *See* Salmon Report at 223; Defendants' Sept. 21 *Daubert* Hearing Tr. at 78.

Dr. Salmon's lifetime cumulative exposure levels are set forth in the table below. As seen below in the second column, Dr. Salmon derives the lifetime cumulative exposure numbers for gastric and esophageal cancers from the De Stefani and Keszei dietary studies. Dr. Salmon derives the lifetime cumulative exposure numbers for bladder, pancreas, and liver cancers from Hidajat. The third column shows Dr. Salmon's estimates of total lifetime NDMA consumption for the subjects in those studies. And the fourth column shows the estimated increased risk of cancer related to those subject's consumption of NDMA, with the fifth column showing the associated confidence interval.

Site	Author	mg NDMA	OR	CI
All	Loh	2.17	1.14	1.03, 1.27
Gastric	De Stefani et al., 1998	3.2	3.62	1.36 - 3.18
Esophagus	Keszei	4.09	1.57	1.13 - 5.23
Bladder	Hidajat	8.70	2.82	1.19 - 2.07
Pancreas	Hidajat	8.70	1.59	1.18 - 2.15
Liver	Hidajat	15.00	1.96	1.16 - 3.29

Salmon Report at 221.

Second, Dr. Salmon estimates the number of years a Plaintiff would have to ingest ranitidine to reach the lifetime cumulative exposure levels referenced in the table above. Dr. Salmon's estimations rely upon an assumption pertaining to the amount of NDMA a Plaintiff ingests through ranitidine on a daily basis, and he ultimately relies upon four different assumptions.

See id. at 223; Defendants' Sept. 21 *Daubert* Hearing Tr. at 78. The four assumptions display a wide range of potential levels of NDMA in ranitidine, as shown in the table below.

At the lowest end of the range, Dr. Salmon assumes that the baseline level of NDMA in ranitidine is equal to the maximum amount of NDMA reported by the FDA and the Defendants' baseline testing combined.[153] With this calculation, using gastric cancer as an example, it would take 10.08 years for a Plaintiff to reach the lifetime cumulative exposure level. Next, Dr. Salmon again assumes the maximum amount of NDMA reported by the FDA and the Defendants' baseline testing, but then adds an additional amount of NDMA. The additional amount of NDMA comes from Emery Pharma's consumer storage testing results. With this calculation, it would take 4.03 years for a Plaintiff to reach the lifetime cumulative exposure level. In yet a third calculation, Dr. Salmon assumes that the baseline level of NDMA in ranitidine is equal to Emery Pharma's baseline testing overall average results. With this calculation, it would take 4.99 years for a Plaintiff to reach the lifetime cumulative exposure level. At the fourth and highest end of the range, Dr. Salmon goes a step further and adds the additional amount of NDMA from Emery Pharma's consumer storage testing results to the Emery Pharma baseline testing results. With this calculation, it would take 1.42 years for a Plaintiff to reach the lifetime cumulative exposure level. Dr. Salmon's calculations are set forth in the following table from his report:

[153] Dr. Salmon inaccurately refers to these numbers as "FDA Max," even though he relies upon some of the numbers from the Defendants' testing.

		Baseline		After consumer storage	
	Study cumulative mg	**FDA max**	**Emery overall average**	**FDA max after consumer storage**	**Emery average after consumer storage**
NDMA, mg/year		0.31755	0.64167	0.79	2.2557787
Site		Years to reach significance			
All	2.17	6.83	3.38	2.73	0.96
Gastric	3.2	10.08	4.99	4.03	1.42
Esophagus	4.09	12.88	6.37	5.15	1.81
Bladder	8.70	27.40	13.56	10.96	3.86
Pancreas	8.7	27.40	13.56	10.96	3.86
Liver	15.0048	47.25	23.38	18.90	6.65

Salmon Report at 223.

In summary, according to the Plaintiffs, Dr. Salmon's final threshold dose opinions are that ranitidine ingestion "is at least causal" for the development of cancer after the following exposure periods: 1.42 years for gastric cancer, 1.81 years for esophageal cancer, 3.86 years for bladder cancer, 3.86 years for pancreatic cancer, and 6.65 years for liver cancer. *See* Defendants' Sept. 22 *Daubert* Hearing Tr. at 22; *see also* Salmon Report at 222-23. These calculations assume that the average ranitidine user takes two doses of 150 mg of ranitidine per day.[154] In addition to his own analyses, Dr. Salmon asserts that Wang found a statistically significant risk of liver and gastric cancers after only one year of ranitidine use of 300 mg per day and that Cardwell found a statistically significant increase in risk of bladder cancer after three years of ranitidine use of 300 mg per day. Salmon Supplemental Report at 4.

b. **Parties' Arguments**

The Defendants argue that Dr. Salmon's dose-response relationship and threshold dose opinions are unreliable for two reasons. First, the Defendants contend that Dr. Salmon relies upon inadmissible studies, such as Hidajat. Second, the Defendants contend that Dr. Salmon's

[154] The Plaintiffs also argue that ranitidine could still cause cancer at lower amounts. Defendants' Sept. 22 *Daubert* Hearing Tr. at 22-23.

methodology is unreliable because, among other reasons, he cherry picks data from the studies that showed a positive dose-response relationship, while deliberating omitting all studies that showed no dose-response relationship. DE 5699 at 103-105 (emphasis omitted); Defendants' Sept. 21 *Daubert* Hearing Tr. at 168. In addition, the Defendants contend that Dr. Salmon deviates from his risk analysis methodology and utilizes an unprecedented method to combine the results across studies. DE 5699 at 104.[155] Dr. Salmon makes speculative assumptions to calculate the NDMA in ranitidine, by combining the FDA's maximum measurements with the Defendants' measurements and then speculating that every exposure to ranitidine was equal to that level of NDMA. Defendants' Sept. 21 *Daubert* Hearing Tr. at 175; Salmon Report at 223.

The Plaintiffs respond that Dr. Salmon uses reliable studies and a reliable methodology. The Plaintiffs argue that Dr. Salmon does not rely upon data from most of the ranitidine studies because those studies lacked relevant data. DE 5915 at 102. In selecting his studies, Dr. Salmon follows the WHO's methodology. *Id*; Defendants' Sept. 21 *Daubert* Hearing Tr. at 245-46. The Plaintiffs also argue that Dr. Salmon did not use pooled dose-response slopes for his dose-response assessment but rather used them for illustrative purposes only. *Id.* at 247. The Plaintiffs conclude that Dr. Salmon follows the WHO's methodology and "calculated dose response slopes from the statistically significant findings from human epidemiologic studies which provided quantitative NDMA amounts." DE 5915 at 102; Defendants' Sept. 21 *Daubert* Hearing Tr. at 245-46.[156]

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[155] The Defendants assert that when asked about this methodology at his deposition, Dr. Salmon admitted he could not name anyone else in the scientific community who has used his methodology. Defendants' Sept. 21 *Daubert* Hearing Tr. at 170.

[156] The Plaintiffs also contended at oral argument that the Defendants should be precluded from raising their argument as to Dr. Salmon and Dr. Panigrahy's cumulative exposure opinions. Defendants' Sept. 21 *Daubert* Hearing Tr. at 80, 239-40. The Court rejects this argument. The Defendants included a section in their Epidemiology Motion, in which they argued that "Dr. Salmon's 'Dose-Response' Analysis is Facially Unreliable." *See* DE 5699 at 103; *see also* Defendants' Sept. 21 *Daubert* Hearing Tr. at 166.

c. **Analysis**

The Court concludes that Dr. Salmon's methodology is unreliable for the seven reasons set forth below:

First, Dr. Salmon relies upon Hidajat and dietary studies for his lifetime cumulative exposure levels, threshold dose opinion, and dose-response relationship opinion. *See* Salmon Report at 221-23; Defendants' Sept. 22 *Daubert* Hearing Tr. at 22-25; Panigrahy Report at 189-91. The Court previously excluded expert opinions premised upon those studies. *See supra* Section VI(A)(3)(b)(iii). Every aspect of an expert's dose-response relationship analysis must be reliable, including "his methodology, the combination of facts and scientific evidence on which he relies, and the links between the evidence and his conclusions." *In re Abilify*, 299 F. Supp. 3d at 1311-12. For this reason alone, Dr. Salmon's dose-response relationship and threshold dose opinions are not reliable.[157]

Second, Dr. Salmon relies upon Emery Pharma's consumer experience testing for his years of exposure calculations, threshold dose opinion, and dose-response relationship opinion. *See* Salmon Report at 221-23; Defendants' Sept. 22 *Daubert* Hearing Tr. at 22-25; Panigrahy Report at 189-91. The Court previously excluded expert opinions premised upon Emery Pharma's testing. *See supra* Section V(A)(1). For this reason alone, Dr. Salmon's dose-response relationship and threshold dose opinions are not reliable.[158]

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[157] Dr. Salmon's unreliable application of the dietary studies to this case is demonstrated, for example, in how Dr. Salmon used the De Stefani study in his analysis of gastric cancer. To compute a lifetime cumulative exposure level, Dr. Salmon relies upon De Stefani's data for 79 hospitalized Uruguayan (mostly) men who completed a dietary questionnaire, together with Dr. Salmon's assumptions that each man began to eat as an adult at age 10, never altered his diet throughout the course of his life, developed cancer at age 65, and did not develop cancer from his carcinogenic-rich diet, even though the conclusion of the study's authors was the "suggestion" that they had found an association between red meat and cancer. Salmon Report at 64-65, 221, 223 (containing a scrivener's error and reporting the risk rate as 3.62 instead of 2.07); De Stefani et al., *supra*, at 161.

[158] Dr. Salmon's unreliable application of NDMA testing to this case is demonstrated, for example, in Dr. Salmon's usage of "maximum" values for NDMA testing in lieu of average values; the Plaintiffs frame the general causation

Third, Dr. Salmon relies upon animal data for his dose-response relationship opinion. For all of the reasons set forth in Section VII(A), *infra*, the animal data addressed in that Section cannot form the basis of a reliable methodology with which to answer the general causation question in this MDL.

Fourth, the Plaintiffs have not shown that Dr. Salmon's methodology has widespread or general acceptance in the scientific community. That is, neither the Plaintiffs nor Dr. Salmon have affirmatively demonstrated that Dr. Salmon calculates his lifetime cumulative exposure values or years of exposure values according to a generally accepted methodology. Nor has Dr. Salmon shown that other parts of his methodology have widespread acceptance in the scientific community. *See supra* Section VI(A)(3)(a).

Fifth, Dr. Salmon uses only certain data from studies showing a positive dose-response relationship and omits data from studies showing either no dose-response relationship or a negative dose-response relationship.[159] *See* Salmon Report at 221-23. This practice indicates a results-driven methodology. The Plaintiffs' explanation that Dr. Salmon follows the WHO's methodology for calculating dose-response relationship does not remedy these deficiencies because regulatory agency methodologies and analyses generally utilize a more conservative calculus than those applicable in tort law. *See infra* Section VII(B).

Sixth, it is not even clear that Dr. Salmon follows the WHO's methodology. The Plaintiffs state in their Response that Dr. Salmon followed a methodology "*like* the principles used by WHO

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question upon "realistic" NDMA levels, but it is not realistic to assume that every pill contained the *maximum* amount of NDMA ever found by reliable testing. If Dr. Salmon had used average values instead of maximum values in his calculations, the amount of time necessary to reach his lifetime consumption values would be 30 years for gastric cancer, 39 years for esophageal cancer, 82 years for bladder and pancreatic cancer, and 141 years for liver cancer. Ranitidine was only available for purchase for 39 years. *Compare* Salmon Report at 212 *with* Salmon Report at 223.

[159] The Plaintiffs' assertion that their experts' dose-response calculations are reliable because they rely only upon statistically significant data points showing a positive dose-response relationship is additionally internally inconsistent with their prior assertions that statistical significance is not a prerequisite of reliability. *See supra* Sections VI(A)(4)(a), (c).

that provide 'if several studies exist, . . . the best representative study should be selected, or several risk estimates evaluated.'" DE 5915 at 102 (emphasis added). The Plaintiffs then cite the WHO Air Quality Guidelines and explain that "a dose-response relationship is usually supported by statistically significant differences between dosed and control groups versus where the response is not statistically significant which would indicate that the exposure level 'is without biologically significant adverse health effects.'" *Id.* at 102 n.257 (citing WHO, *Air Quality Guidelines: Criteria Used in Establishing Guideline Values* 10 (2000); *Environmental Health Criteria 240: Dose-Response Assessment and Derivation of Health-Based Guidance Values* 9-10 (2020)). The passage from the WHO Air Quality Guidelines suggests that a positive dose-response relationship generally requires statistically significant, positive data. Therefore, rather than supporting the Plaintiffs' positions that Dr. Salmon follows the WHO's methodology and that his methodology is reliable, their reference underscores the results-driven nature of Dr. Salmon's methodology.

Seventh and finally, Dr. Salmon applies internally inconsistent principles to analyze the data in Cardwell and Wang. *See supra* Sections VI(A)(3), (4). For all of the reasons set forth in the Court's prior discussion on that topic, Dr. Salmon's internally inconsistent analysis of available data suggests an unreliable, results-driven methodology.

Thus, based on the totality of the evidence, the Plaintiffs have not met their burden to show that Dr. Salmon's dose-response relationship and threshold dose opinions are reliable.

2. Remaining Experts' Dose-Response Relationship Opinions

The Court turns to the Plaintiffs' remaining general causation experts. Five of the Plaintiffs' experts—Drs. Najafi, Davis, Marletta, Melnick, Le, and Michaels[160]—do not provide

[160] While Dr. Le notes in her report that a few studies showed a dose-response relationship, she does not provide a clear opinion as to whether and how ranitidine exhibits a positive dose-response relationship for any of the Designated Cancers. Moreover, the Plaintiffs did not argue that Dr. Le provides a dose-response opinion. *See* Le Report at 87,

opinions on whether the amount or duration of exposure to ranitidine affects the risks of developing any of the five Designated Cancers. Given their failure to opine on the correlation between dosage and disease, the experts do not provide primary evidence of dose-response relationship. The Court now addresses the Plaintiffs' experts' dose-response relationship opinions and related threshold dose opinions.

a. **Summaries of Drs. McTiernan, Moorman, and Panigrahy's Opinions**

Dr. McTiernan. According to Dr. McTiernan, ranitidine exhibits a dose-response relationship for all five Designated Cancers. She states that dose-response relationship was not "directly assessed" in the ranitidine epidemiological studies for bladder, esophageal, or stomach cancer. McTiernan Report at 203. Dr. McTiernan opines that in Cardwell "use of ranitidine for 3 years or longer showed higher effects on bladder cancer risk than did use overall." *Id.* Dr. McTiernan opines that in McDowell, which showed that "the risk for more than 6 prescriptions was slightly lower than that for 1-6 prescriptions" for pancreatic cancer. *Id.* at 254. She states that "[t]his suggests a threshold effect, or that number of prescriptions was not an adequate proxy of total exposure, which would require knowing dose, frequency, and duration of use." *Id.*

Dr. McTiernan further opines that studies of NDMA exposure from rubber manufacturing (including Hidajat) showed a dose-response relationship for esophageal, liver, pancreatic, and stomach cancers. *Id.* at 222, 236, 254, 283. She opines that a "[s]trong dose-response was seen with NDMA exposure in rubber manufacturing but not with increased exposure to nitrates in the fertilizer industry" for bladder cancer. *Id.* at 203. Dr. McTiernan opines, that in addition to rubber manufacturing studies, a dose-response relationship "was suggested in the Freedman study on

101-102, 108. Also, although Dr. Michaels makes a brief reference to Cardwell on page 64 of his expert report in a discussion about dose-response relationship, the Court concludes that this is not a dose-response relationship opinion. In the alternative, it is insufficient to be reliable under *Daubert*.

nitrates, nitrites, and liver." *Id.* at 236. Finally, Dr. McTiernan opines that dose-response relationship was observed "only in one of the nitrate fertilizer studies" and in the meta-analyses of NDMA and nitrite intake conducted by Song and Zhang for stomach cancer. *Id.* at 283.

In her supplemental report that addressed the Wang study, Dr. McTiernan states:

> The dose-response analysis showed clear evidence of increasing liver cancer risks with increase total dose (daily defined dose, DDD) . . . . For stomach cancer, there was a trend toward increasing risk with increasing dose . . . . Clear dose-response relationships were not seen for pancreas cancer. Neither esophageal nor bladder cancers were presented for dose-response."

McTiernan Supplemental Report at 3. Dr. McTiernan concludes that Wang strengthened her dose-response relationship analysis and overall general causation opinions for liver and stomach cancers. *Id.* at 10.

Dr. Moorman. Dr. Moorman relies primarily upon studies of dietary and occupational NDMA exposure to form her dose-response relationship opinions. She states:

> Although dose-response analyses are important for making causal assessments, it is important to note that the data were inadequate for making such an assessment of the risk of cancer in relation to long-term use of ranitidine in nearly all of the ranitidine epidemiologic studies. As noted above, dose-response information is available in dietary and occupational studies of NDMA exposure, and these data were part of my evaluation of dose-response trends.

Moorman Report at 48. Dr. Moorman makes an exception for Cardwell, opining that Cardwell exhibited "a significant dose-response trend with increasing use whether evaluated as the number of prescriptions . . . or the number of defined daily doses" for bladder cancer. *Id.* at 87. In her supplemental report, Dr. Moorman opines that Cardwell reported a statistically significant increased risk for bladder cancer risk with three years of ranitidine use at 300 mg per day. Moorman Supplemental Report at 4. Dr. Moorman also opines that Hidajat and dietary studies of NDMA indicate a positive dose-response relationship for bladder cancer. Moorman Report at 112, 116. Dr. Moorman opines that dietary and occupational studies of NDMA support a finding of a

dose-response relationship for pancreatic cancer. *Id.* at 139. Similarly, for liver cancer, Dr. Moorman states:

> The data for evaluating a dose-response relationship in the ranitidine studies is limited, which precludes one from making a conclusion about biological gradient from these studies. There is more evidence of a dose-response relationship with NDMA exposure from dietary and occupational studies, although such trends were not apparent in all studies, which is not surprising given the challenges of accurately assessing dietary variable.

Moorman Report at 163. Dr. Moorman also concludes that occupational and dietary studies of NDMA provides evidence of a dose-response relationship for esophageal and stomach cancers. *Id.* at 197, 229.

In her supplemental report addressing the Wang study, Dr. Moorman opines that positive dose-response relationships were reported for liver and gastric cancers, though the trend was clearer for liver cancer. Moorman Supplemental Report at 3. She stated that "a clear dose-response trend was not apparent for pancreatic cancer." *Id.*

Dr. Panigrahy. Dr. Panigrahy relies primarily upon animal studies and Hidajat to opine that NDMA exhibits a dose-response relationship. Panigrahy Report at 189-97. He stated, "[g]iven the depth of animal studies, which is reinforced by the Hidajat study in human participants, the evidence is overwhelming that NDMA exhibits a classic dose-response." *Id.* at 191. Dr. Panigrahy explains that Hidajat found that increasing NDMA exposure was associated with statistically significant increased risks of death for each of the five Designated Cancers. *Id.* at 195. Like Drs. Moorman and McTiernan, Dr. Panigrahy opines that Cardwell shows that participants using ranitidine for more than three years have a statistically significant increased risk of bladder cancer compared to nonusers. *Id.* at 210.

b. **Parties' Arguments and Analysis**

The Defendants argue that Drs. Panigrahy, Moorman, and McTiernan's dose-response relationship opinions are unreliable because they base their calculations on inadmissible studies and they utilize unreliable methodologies. *See* Defendants' Sept. 22 *Daubert* Hearing Tr. at 204. The Plaintiffs deny both claims.

Here, Drs. McTiernan, Moorman, and Panigrahy rely in part upon the data from Hidajat and dietary studies of NDMA, and Dr. Panigrahy relies upon animal studies. However, expert opinions based on those studies are unreliable. *See* Sections VI(A)(3)(b)(iii), VII(A). Additionally, Drs. McTiernan and Moorman apply internally inconsistent principles to analyze the data in Cardwell and Wang; each selectively extract data points from the studies while disregarding other data points from the same studies without justification; and each deviate from the study authors' conclusions. *See supra* Sections VI(A)(3), (4). For these reasons, the dose-response relationship opinions of Drs. McTiernan, Moorman, and Panigrahy are not reliable.[161]

3. Drs. Panigrahy, Michaels, McTiernan, and Moorman's Threshold Dose Opinions

The Court now addresses the Plaintiffs' remaining experts' threshold dose opinions. Two of the Plaintiffs' experts—Drs. Le and Melnick—concede that they do not offer opinions as to whether there is a threshold dose at which NDMA is not carcinogenic in humans. *See* Le Tr. at 253-54; Melnick Dep. at 292-93. As detailed above, Dr. Salmon provides a threshold dose opinion based upon Hidajat, Wang, dietary studies of NDMA, and the results of Dr. Najafi's consumer storage testing. Four of the Plaintiffs' experts—Drs. Panigrahy, Michaels, McTiernan, and Moorman—opine that there is no threshold amount of NDMA that does not cause cancer.

[161] The Plaintiffs' epidemiologists' dose-response relationship opinions are derived solely from the epidemiology in this case. The Court is not aware of any non-epidemiological evidence upon which the Plaintiffs' epidemiologists rely to formulate their dose-response opinions.

Panigrahy Report at 191-92; McTiernan Dep. 605-06; Moorman Dep. 288-90; Michaels Report at 3, 62-63. While they also cite levels at which NDMA can cause cancer based on Cardwell and Wang, they do not opine that these levels are minimum threshold dose levels. Dr. Panigrahy opines, based on data from Hidajat and Emery Pharma, that a person taking two tablets of ranitidine each day can reach a cumulative NDMA-exposure level of 5,990 micrograms and increase his risk of cancer significantly in 7.5 years for stomach, bladder, esophageal, and pancreatic cancers and in 14.3 years for liver cancer. Panigrahy Report at 198-99; Defendant's September 22 *Daubert* Hearing Tr. at 235.

In this section, the Court summarizes the parties' arguments on Drs. Panigrahy, Michaels, McTiernan, and Moorman's "no threshold dose" opinions and analyzes the admissibility of these opinions.

a. **Parties' Arguments**

The Defendants present many arguments as to why the Court should reject the "no-threshold" theory. The Defendants argue that the no-threshold theory has been widely rejected by federal courts—the Plaintiffs are required to provide a dose at which NDMA becomes toxic in order to meet their general causation burden. *See* DE 5696 at 25; *see also* Defendants' Sept. 22*Daubert* Hearing Tr. at 212-13. They also argue that the no-threshold theory is unreliable because it cannot be falsified or validated, *see* DE 5696 at 25, and it "'flies in the face of the scientific literature' that there are doses of NDMA at which 'you do not see a statistically significant risk of developing' cancer," *see id.* (internal citations omitted), as, they argue, is consistent with the FDA's ADI limit for NDMA.

The Plaintiffs respond, on the one hand, that they are not required as a matter of law to provide a threshold dose below which ranitidine does not cause cancer. *See, e.g.*, Defendants'

Sept. 22 *Daubert* Hearing Tr. at 233-35 ("Not a single case says Plaintiffs must identify the minimum threshold dose, not precisely, not in a range, not at all."). The Plaintiffs rely upon Ninth Circuit precedent to argue that they are only required to establish that the highest dose that any Plaintiff could have reasonably been exposed to can cause the Designated Cancers. *See id.* at 231-32.[162] Consistent with this position, the Plaintiffs argue (in the "Facts" section of their brief) that "[t]he opinions shared by Dr. Panigrahy, Dr. Michaels, Dr. McTiernan, and Dr. Moorman that there is no threshold safe dose of NDMA are tethered to the established science in this case and are well-founded." DE 5913 at 14. They claim that Peto, a study in which NDMA was administered to rats to evaluate whether there is a dose-response relationship, confirmed that NDMA does not have a threshold for tumor induction. *See* Richard Peto et al., *Effects on 4080 Rats of Chronic Ingestion of* N-*nitrosodiethylamine or* N-*nitrosodimethylamine: A Detailed Dose-Response Study*, 51 Cancer Rsch. 6415, 6440 (1991). For further support, the Plaintiffs cite to GSK's report which states that "'NDMA is a genotoxic carcinogen, and exposure should be reduced to the extent possible,' because it is 'highly likely that NDMA is carcinogenic to humans potentially at low levels of exposure.'" *Id.* at 15 (footnote omitted).

On the other hand, the Plaintiffs argue that their experts "did not opine on the legal question of threshold dose, but merely testified as to the scientific reality that any amount of a carcinogen is dangerous." *Id.* at 26. They state that Dr. McTiernan did not opine on threshold dose for any of the Designated Cancers, *id.* at 26, and that the Defendants mischaracterized the testimony of Drs. Michaels, Moorman, and Panigrahy to make it seem as though they "all gave an opinion as to what amount of NDMA suffices to establish a *legal* causation threshold" when they did not. *Id.* at 27.

[162] The Plaintiffs assert that they will have the opportunity at the specific causation stage of this litigation to show that lower doses of NDMA can also cause the Designated Cancers. *See* DE 5915 at 57 ("Here, the question for general causation is whether NDMA can, without regard to dose, cause cancer, and it certainly can. Dose is a separate question; a specific causation question."); *see also* Defendants' Sept. 21 *Daubert* Hearing Tr. at 193; *supra* Section IV.

The Plaintiffs characterize Drs. Michaels, Moorman, and Panigrahy's opinions as "merely testif[ying] as to the same scientific reality that GlaxoSmithKline recognized in its 2019 Hazard Assessment Report: 'NDMA is a genotoxic carcinogen, and exposure should be reduced to the extent possible.'" *Id.* (citation omitted).

And, in the alternative, the Plaintiffs argue that Drs. Panigrahy, McTiernan, and Moorman did in fact provide doses at which ranitidine can cause cancer, just with the caveat that lower doses could still cause cancer, too. *See* Defendants' September 22 *Daubert* Hearing Tr. at 225, 244-46.

b. **Analysis**

The Eleventh Circuit is clear that the Plaintiffs are required to provide a threshold dose at which ranitidine becomes toxic to humans to meet their general causation burden. *See supra* Sections IV, VI(A)(3)(b)(iii). That threshold dose is a potential floor for whether the specific dose a Plaintiff was exposed to was enough to cause his cancer at the specific causation stage. Without a determination of the threshold dose, a topic integral to general causation, the Plaintiffs would litigate threshold dose at the specific causation stage, even though case law is clear that threshold dose is part of the general causation inquiry. The Court proceeds to determine whether the Plaintiffs have provided a threshold dose at which ranitidine can cause the Designated Cancers.

The Court rejects the Plaintiffs' attempt to recharacterize their experts' no-threshold opinions as "merely" a "scientific reality" rather than a "legal opinion on threshold dose." General causation experts are not tasked with providing legal opinions or legal analysis. Rather, a general causation expert's role is to provide a *scientific* opinion supported by the available facts or data. The party offering the expert has the burden to show that their expert's scientific opinion is admissible. Here, the Plaintiffs' experts' testimony that there is not a threshold dose at which NDMA does not cause cancer falls squarely within the experts' role to provide an opinion on the

amount of NDMA exposure that can cause cancer in humans. The Plaintiffs have the burden to show that their experts' no-threshold opinions are admissible.

The Plaintiffs have not met their burden to show that their experts' no-threshold opinions are admissible. Even if the no-threshold opinions were sufficient, the Plaintiffs nonetheless have failed to establish the admissibility of their experts' no-threshold opinions. First, the Plaintiffs inaccurately characterize as "facts" their arguments relating to their experts' no-threshold opinions. Such a characterization implies that the Court simply should accept the Plaintiffs' experts' no-threshold opinions without any analysis as to their admissibility. The Court's role is to serve as a gatekeeper and to ensure that unreliable and unhelpful evidence does not reach the jury. *See McClain*, 401 F.3d at 1237. As such, the Court proceeds to evaluate the Plaintiffs' arguments regarding their experts' no-threshold opinions.

The Plaintiffs have failed to evaluate any of the *Daubert* factors which bear upon the admissibility of their experts' no-threshold opinions. The Plaintiffs assert that it is generally accepted in the scientific community that NDMA is carcinogenic, DE 5913 at 14, but this argument does not support a finding that it is generally accepted in the scientific community that there is no dose at which NDMA does not cause cancer in humans.

The Plaintiffs' contention that Defendant GSK acknowledged that NDMA is carcinogenic also is insufficient to establish that a no-threshold theory of exposure is generally accepted in the scientific community. *See id.* at 15. The Plaintiffs quote an internal GSK document which states that it is "*highly likely* that NDMA is carcinogenic to humans *potentially* at low levels of exposure." *Id.* (quoting DE 5912 Ex. 41 (GSK Health Hazard Report (GSKZAN0003419540))). The language is not conclusive, and "low levels of exposure" do not equate to "no threshold."

These arguments do not support the conclusion that it is generally accepted in the scientific community that there is no dose at which **ranitidine** does not cause cancer.

Finally, despite Drs. Panigrahy, McTiernan, and Moorman's no-threshold opinions, they each rely upon Cardwell and Wang to opine that NDMA can cause cancer after three years of daily consumption of 300 mg ranitidine. Dr. Panigrahy also relies upon Hidajat to opine that the same exposure can cause stomach, bladder, esophageal, and pancreatic cancers after 7.5 years and liver cancer after 14.3 years. But, these opinions are derived from unreliable methodologies and they are not reliable evidence of threshold dose. *See supra* Sections VI(A)(3)-(4), VI(B)(1).

In conclusion, based on Eleventh Circuit precedent on no-threshold dose opinions and the totality of the evidence, the Plaintiffs' experts' threshold dose opinions are unreliable evidence of a dose-response relationship. The Plaintiffs' experts are precluded from offering opinions that there is no threshold dose below which either NDMA or ranitidine does not cause cancer in humans.

None of the Plaintiffs' experts have provided reliable primary evidence of dose-response relationship for ranitidine. The Plaintiffs' experts either fail to address dose-response relationship or provide dose-response relationship opinions derived from unreliable methodologies. Furthermore, the Plaintiffs' experts have not provided reliable opinions regarding what threshold dose of NDMA causes each of the five Designated Cancers, let alone what threshold dose of ranitidine causes cancer. Based upon the totality of the evidence, none of the Plaintiffs' experts provided reliable primary evidence of a dose-response relationship for ranitidine and the Designated Cancers. The lack of reliable dose-response relationship opinions casts doubt on the reliability of the Plaintiffs' experts' general causation methodologies.

C. Background Risk

Unlike with dose-response relationship, for which the Court received a small amount of briefing, the parties did not provide the Court with any briefing on the third and final type of "primary" evidence, background risk. The Court presumed that the reason it received no briefing was because no Plaintiffs' expert formulated a background-risk-based opinion. At oral argument, however, the Plaintiffs contended that their experts did formulate background risk opinions. For that reason, the Court proceeds to analyze background risk below.

In addition to epidemiology and dose-response relationship, the Eleventh Circuit has deemed background risk of disease to be primary evidence of general causation. *Chapman*, 766 F.3d at 1308. Background risk "is the risk a plaintiff and other members of the general public have of suffering the disease or injury that plaintiff alleges without exposure to the drug or chemical in question. 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 (emphasis omitted). "An expert must know the background prevalence of a disease before he can determine whether the risk of that disease is increased as a result of exposure to the agent." *In re Abilify*, 299 F. Supp. 3d at 1308. Background risk is important because it establishes a baseline for disease incidence; without a baseline, any incidence of disease in exposed individuals could be mere coincidence. *See In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d at 1356.

Both the Plaintiffs and the Defendants failed to brief the question of whether the Plaintiffs' experts accounted for the background risks of the Designated Cancers. The Court asked the parties to be prepared to discuss the issue of background risk at oral argument.

On the first day of oral argument, the Plaintiffs argued that their experts provided opinions regarding background risk. Defendants' Sept. 21 *Daubert* Hearing Tr. at 67-68; *see also*

Defendants' Sept. 22 *Daubert* Hearing Tr. at 200. On the second day of oral argument, the Plaintiffs conceded that they did not argue background risk in their Response because the Defendants did not address background risk in their briefing. Defendants' Sept. 22 *Daubert* Hearing Tr. at 237-38. Further, the Plaintiffs argued that, because their experts did opine as to background risk, and because those opinions were unchallenged, "that alone means that we prevail." *Id.*

The Court finds that the Defendants did present an argument that the Plaintiffs' experts failed to opine on background risk when they asserted that the Plaintiffs lacked epidemiological evidence and that they were entitled to summary judgment. *See* DE 5696 at 5. For the Defendants to be entitled to summary judgment, the Plaintiffs must lack all forms of primary evidence. Thus, the Defendants argued by implication that the Plaintiffs had no reliable evidence of background risk. It was therefore incumbent upon the Plaintiffs to argue that they did have reliable evidence of background risk and as such had primary evidence to defeat summary judgment. They failed to do so.

The Court gave the Plaintiffs an opportunity during oral argument to identify where in the record their experts provide background risk opinions. The Plaintiffs said that Drs. Moorman and McTiernan provided analyses of background risk in certain passages of their reports.[163] Defendants' Sept. 22 *Daubert* Hearing Tr. at 207.

The Court has examined those passages and concludes that they do not constitute reliable evidence of background risk. The passages do not contain analyses of background risk evidence; they do not provide any information about the general public's risks of developing a Designated Cancer without exposure to ranitidine; they do not provide the overall background rates of any of

[163] The Plaintiffs pointed to Dr. Moorman's report at pages 12-13, and to Dr. McTiernan's report at pages 28, 32, 64, 161, 213, and 219. Defendants' Sept. 22 *Daubert* Hearing Tr. at 207.

the five Designated cancers; and they do not provide any of the other potential causes of the Designated Cancers. Although one passage compares risk rates for esophageal cancer, it compares the risk that rubber workers, not ranitidine users, have of developing esophageal cancer to the risk in the general population. McTiernan Report at 161.

For the foregoing reasons, the Plaintiffs' experts do not offer background-risk-based opinions, which is consistent with their lack of briefing on the subject. In the alternative, the few references to background risk in the Plaintiffs' experts' reports do not constitute a reliable methodology because they do not meet any of the *Daubert* factors. Also in the alternative, even if the comparisons of risk rates cited by the Plaintiffs' experts constitute a reviewable background risk methodology, it is not a *reliable* methodology. *See supra* Section VI(A)(3)(b)(iii); *see also In re Abilify*, 299 F. Supp. 3d at 1311-12.

D. Conclusion on Plaintiffs' Primary Evidence

Therefore, based upon a review of the totality of the evidence, the Plaintiffs have not met their burden to show that their experts relied upon any form of reliable primary evidence in support of their general causation opinions. Because the Plaintiffs lack primary evidence, under Eleventh Circuit case law, all of the Plaintiffs' general causation experts are stricken, and the Defendants are entitled to summary judgment. The Plaintiffs cannot support their general causation opinions with secondary evidence alone. *See Chapman*, 766 F.3d at 1308; *In re Abilify*, 299 F. Supp. 3d at 1306; *supra* Section VI.

The Court discussed the Plaintiffs' secondary evidence in the context of the amount of NDMA at issue in this MDL. *See supra* Section V. The Plaintiffs' experts also rely upon secondary evidence to support their position that ranitidine causes cancer. Given the Plaintiffs' lack of primary evidence, the Court does not need to analyze the remainder of the Plaintiffs' secondary

evidence. However, the Court turns to the Plaintiffs' other secondary evidence for two reasons. First, the Court considers secondary evidence because the Defendants have moved to exclude certain types of the secondary evidence. Also, because secondary evidence can bolster primary evidence under Eleventh Circuit case law, *see In re Seroquel*, 2009 WL 3806435, at *7-8, the Court considered secondary evidence as part of the totality of the evidence, in ruling upon the Plaintiffs' primary evidence.

VII. Secondary Evidence of General Causation

In the following section, the Court reviews and analyzes other secondary evidence that the Plaintiffs' experts rely upon in forming their general causation opinions. First, the Court considers the Plaintiffs' experts' reliance on animal studies and then the Plaintiffs' experts' reliance on the FDA's regulatory risk assessments.[164]

A. Animal Studies

The Plaintiffs' experts have a theory[165] about how the NDMA in ranitidine caused the Plaintiffs' cancer. To prove that theory and to prove that, in general, ranitidine causes cancer, nine

[164] The Court does not consider the mechanistic *in vitro* studies and the IARC 10 Key Characteristics of Carcinogens upon which the Plaintiffs' experts relied. In their Response, the Plaintiffs assert generally that their experts rely upon "various mechanistic evidence," including the *in vitro* studies and the IARC 10 Key Characteristics of Carcinogens. DE 5913 at 24. The Plaintiffs' only argument on why relying upon this secondary mechanistic evidence constitutes a reliable methodology is that their experts considered this evidence as part of their weight-of-the-evidence methodologies. *Id.* The Plaintiffs' mere assertion that their experts followed weight-of-the-evidence methodologies is insufficient to carry their burden that their experts' opinion is reliable. *See supra* Section V(B)(1).

[165] They offer the following mechanism of cancer causation for NDMA: after oral ingestion of NDMA, it is rapidly absorbed (>90%) and enters the bloodstream. Once in the bloodstream, NDMA distributes extensively into many organs throughout the body. NDMA then induces cancer at the sites of those organs by one of two methods. In the first method, NDMA directly activates the RAS oncogenes to induce cancer. In the second method of cancer induction, NDMA is metabolized by the hepatic cytochrome P450 CYP2E1 through a process of denitrosation into methyldiazonium, an alkylating agent that crosslinks to DNA to induce cancer. The Plaintiffs assert that the CYP2E1 is present in the liver, bladder, esophagus, stomach, and pancreas, indicating that cancer can potentially be induced at each of those sites.

of the Plaintiffs' experts rely in part on animal studies.[166] The Defendants argue that the animal study data does not fit the question of general causation in humans.

Fit is required under *Daubert* to ensure that expert evidence is helpful to the jury. The fit element requires an expert to show a science-based connection between the data that the expert relies upon and the opinion she seeks to offer. If a court must make a large inferential leap from the data that the expert relied upon to her conclusion, then the expert's opinion may fail the fit requirement and become inadmissible. Here, first, the Defendants argue that the Plaintiffs' experts fail to account for species extrapolation and dose extrapolation. Second, the Defendants argue that the Plaintiffs' experts improperly extrapolate from findings of one cancer to the other Designated Cancers. The Court considers each argument in turn.

1. Species and Dose Extrapolation

In this section, the Court addresses species and dose extrapolation.[167] Species extrapolation is an inference that a researcher makes when drawing a conclusion about a value in humans based on values observed in a species of animal. Dose extrapolation is an inference that a researcher makes when drawing a conclusion about the dose-response relationship of a substance in humans based on the dose-response relationship of the same substance in a species of animal. Animal studies generally expose their subjects to doses that are much higher than the doses given to humans, and those differences should be accounted for.

Species and dose extrapolation are critical for the animal studies to be helpful in addressing the general causation question in this MDL. For the most part, the parties agree that NDMA is carcinogenic, at least in some animals. If the general causation question in this MDL was "whether

[166] These experts are Drs. Le, Marletta, McTiernan, Melnick, Michaels, Moorman, Najafi, Panigrahy, and Salmon. However, in their motion, the Defendants only challenge four of these experts: Drs. Le, Panigrahy, Salmon, and Melnick.
[167] *See supra* Section V(B)(2)(b)(ii) for a more detailed discussion of extrapolation.

NDMA is carcinogenic to animals," then the Plaintiffs' experts could rely upon animal data (without extrapolating) to opine on general causation. But, that is not the general causation question in this MDL. Here, the question is: "Does the scientific evidence reliably demonstrate that ranitidine is capable of causing a Designated Cancer at the highest realistic exposure level any plaintiff may have experienced?" Therefore, the Plaintiffs can rely upon animal studies to address this question, but only if the experts reliably extrapolate from the animal data. The experts must show that the animal data predicts a human risk of developing a Designated Cancer as a result of ingesting the highest realistic exposure level of NDMA from ranitidine.

The Court carefully reviews and analyzes the parties' arguments on species and dose extrapolation. This fact-intensive review of the parties' arguments includes specific questions such as whether a rodent's metabolism is similar to a human's metabolism. But, it is important to not lose sight of the forest through the trees: if the Plaintiffs' experts fail to connect the animal data to the Plaintiffs' consumption of ranitidine, then the animal data is not a good fit for this MDL.

a. **Parties' Arguments**

The Defendants contend that the Plaintiffs' experts fail to account for species extrapolation and dose extrapolation. DE 5696 at 20-21. The Plaintiffs respond that regulatory agencies and other scientific bodies have utilized animal studies to predict toxic responses in humans. DE 5913 at 11-13, 24. The Plaintiffs assert that regulatory agencies such as IARC, the WHO, the Agency for Toxic Substances and Disease Registry, and the National Toxicology Program have concluded that NDMA is carcinogenic in numerous animal species. *Id.* at 12-13, 24.

Additionally, the Plaintiffs respond to the Defendants' claim that their experts do not explain their species extrapolation by asserting that humans and animals metabolize NDMA similarly. They state that "the WHO concluded, based on metabolic NDMA studies in human

liver preparations, that no qualitative differences existed in the metabolism of NDMA between humans and laboratory animals." *Id.* at 12. They also claim that "[i]t is generally accepted that NDMA is metabolized similarly in human tissue and rodent tissue." *Id.* Moreover, the Plaintiffs conceded at oral argument that their experts do not provide any explanation for how they were able to extrapolate from animal studies to humans on the basis of either species or dose. *See* Defendants' Sept. 22 *Daubert* Hearing Tr. at 180-81.

b. **Analysis**

Experts seeking to rely upon animal studies in support of a general causation opinion must "explain how and why [they] could have extrapolated their opinions" to humans. *Joiner*, 522 U.S. at 144-46 (affirming the exclusion of an expert opinion where failure to extrapolate from animal studies left "too great an analytical gap between the data and the opinion proffered"). Experts must evaluate both species extrapolation and dose extrapolation:

> Animal studies have two significant disadvantages, however. First, animal study results must be extrapolated to another species—human beings—and differences in absorption, metabolism, and other factors may result in interspecies variation in responses. For example, one powerful human teratogen, thalidomide, does not cause birth defects in most rodent species. Similarly, some known teratogens in animals are not believed to be human teratogens. In general, it is often difficult to confirm that an agent known to be toxic in animals is safe for human beings. The second difficulty with inferring human causation from animal studies is that the high doses customarily used in animal studies require consideration of the dose–response relationship and whether a threshold no-effect dose exists.

Reference Manual on Scientific Evidence, *supra*, at 563 (footnotes omitted); *see also Siharath*, 131 F. Supp. 2d at 1366-69. "The expert should review similarities and differences between the animal species in which the compound has been tested and humans. This analysis should form the basis of the expert's opinion regarding whether extrapolation from animals to humans is warranted." *Reference Manual on Scientific Evidence*, *supra*, at 661.

The Court could not find an explanation in the Plaintiffs' Response of how the Plaintiffs' experts extrapolate from their animal studies to humans by either species or dose. At oral argument, the Plaintiffs confirmed that they did not put forward such an explanation. The Court asked the Plaintiffs: "[P]lease tell me whether you explained how and why your experts were able to extrapolate by dose from animal studies to humans based on these definitions." Defendants' Sept. 22 *Daubert* Hearing Tr. at 179-180. The Plaintiffs responded: "Judge, I believe that there is a fairly simple answer to your question. Our experts do not do dose extrapolation from animal data to human data." *Id.* at 180. The Court then asked whether their experts explained how they extrapolated by species. *Id.* at 180-81. The Plaintiffs responded:

> Once again, Your Honor, I don't think our experts extrapolate from animals to apply it to humans, although the IARC does note qualitatively NDMA acts the same in animals and humans. However, the metabolism in animals and humans is very different and we rely on the Gombar studies to look at the viability, of NDMA, but we are not extrapolating and taking those numbers to apply them to humans. We are relying on human epidemiological data and doses to come up with our dose response calculations.

Id.

The arguments that the Plaintiffs make in their briefing regarding their experts' reliance on animal studies, even if construed as extrapolation arguments despite the concession made at oral argument, are insufficient—they do not explain how and why their experts could reliably extrapolate from animal studies to humans. The Court now discusses those arguments.

The Plaintiffs argue that animal studies are a valid means of assessing the toxic response of NDMA in humans because regulatory agencies have utilized animal studies for this purpose and determined that NDMA is carcinogenic in various animals. DE 5913 at 12. There are a number of reasons why this argument does not show how and why the Plaintiffs' experts conducted species or dose extrapolation. First, government agencies typically utilize a lower threshold of proof than is required in tort law because agencies operate from the cautious perspective of preventing public

exposure to potentially harmful substances. *See Mitchell v. Gencorp, Inc.*, 165 F.3d 778, 783 n.3 (10th Cir. 1999). The fact that government agencies have relied upon certain animal studies for preventative purposes does not support a conclusion that those studies are reliable or helpful for the purposes of this litigation.

Second, the Plaintiffs' argument appears "to proceed as if the only issue [is] whether animal studies can ever be a proper foundation for an expert's opinion." *See Joiner*, 522 U.S. at 144 (citation omitted). However, that is not the proper question, as the Defendants do not contest the use of animal studies generally. "The issue [is] whether *these* experts' opinions [are] sufficiently supported by the animal studies on which they purport[] to rely." *Id*. The Plaintiffs' reliance on other institutions' use of animal studies does not substitute for or explain to the Court their experts' own rationale as to why they choose to rely upon the studies, how their methodologies account for the studies, or how the studies inform the relevant questions in this litigation.

The Plaintiffs' second argument, that humans and animals metabolize NDMA similarly, is misleading and fails to explain to the Court why and how the Plaintiffs' experts reliably extrapolate from animal studies. The Plaintiffs' bare assertion that the WHO found "no qualitative differences" in the metabolisms of NDMA between humans and laboratory animals is unhelpful. *See* DE 5913 at 12. It is unclear to which laboratory animals the Plaintiffs refer. Such a generalized statement about laboratory animals as a whole provides no information about the Plaintiffs' experts' ability to rely upon data for a given, particular species to reach conclusions about humans. Regarding rodents specifically, the Plaintiffs state that "[i]t is generally accepted that NDMA is metabolized similarly in human tissue and rodent tissue." *Id.* At oral argument, the Plaintiffs clarified that "[t]he way that the actual cells in the tissues metabolize NDMA in the rat liver is similar to how the human liver metabolizes NDMA," clarifying that both human and rodent livers have the same

cytochrome P450 enzymes that metabolize NDMA. Defendants' Sept. 22 *Daubert* Hearing Tr. at 79.

However, even though the Plaintiffs argue that humans and rats metabolize NDMA similarly, the Plaintiffs and their experts also inconsistently contend that there are many *differences* between human and rat metabolisms that make NDMA more carcinogenic to humans than to rats. The Plaintiffs explain that studies have found inter-species variability in the bioavailability of NDMA when administered orally. DE 5913 at 13. Bioavailability is a measure of the amount of a substance that is absorbed into the bloodstream, where it can then be distributed to other sites in the body to exert its effects. Le Report at 25. Dr. Le explains that bioavailability of NDMA is affected by hepatic first-pass metabolism. *Id.* at 49. First-pass metabolism occurs as part of the process of drug metabolism; after a substance is ingested, it is metabolized in part before it reaches systemic circulation in the body. In other words, a fraction of the substance is lost during the process of absorption and initial metabolization, resulting in only a small portion of the active substance that reaches the circulatory system.

The Plaintiffs argue that when NDMA is administered in low doses to humans, it undergoes extensive first-pass metabolism in the liver prior to reaching systemic circulation. *See* DE 5913 at 13-14. Thus, according to the Plaintiffs, a portion of the dose of NDMA is metabolized at the liver prior to the rest of the dose entering the blood. In support of this argument, the Plaintiffs rely upon animal studies which show a bioavailability of NDMA of 8% in rats, 49% in monkeys, 67% in pigs, and 93% in dogs. *See id.* The Plaintiffs' experts rely upon these studies to opine that humans have a bioavailability of NDMA similar to that of larger experimental animals, and much higher than rodents. *Id.*; *see also* Le Report at 49-52 (concluding that humans have a bioavailability of NDMA over 90%). The Plaintiffs argue that *because* of the differences in human and rat

metabolisms, "NDMA's carcinogenic activity can be more aggressive and result in many more tumor types in humans compared to rodents." DE 5913 at 14. In other words, because 90% of NDMA reaches blood circulation in humans, while only 8% reaches blood circulation in rats, the Plaintiffs' experts opine that NDMA can cause cancer in a greater number of organs in humans than in rats.

The Plaintiffs do not provide a sufficient explanation as to why, despite the differences in the metabolisms of rodents and humans, their experts could still reliably extrapolate from rodents to humans. In fact, Dr. Le's report explicitly cautions against relying on rodent data to infer general causation, stating that "rat data should be interpreted cautiously especially when data for multiple more-evolved species are available." Le Report at 48. The Plaintiffs' experts' bioavailability analyses undermine the Plaintiffs' assertion that their experts can extrapolate from rodents to humans because they have similar metabolisms.

Finally, the Plaintiffs do not explain species extrapolation for any of the other animal species tested in the studies that they rely upon including for monkeys, ducks, frogs, trout, and guppies. The Plaintiffs have not reliably accounted for species extrapolation because they failed to explain a valid scientific connection between the animal species tested and humans and they made contradictory statements regarding the similarities between rodent metabolisms and human metabolisms.

The Plaintiffs also fail to account for dose extrapolation. The Plaintiffs make two arguments in their Response on the subject of dose extrapolation. The Plaintiffs claim that "all available data supports a consistent dose response between NDMA and cancer." DE 5913 at 11. The Plaintiffs also assert that Peto, a study of NDMA carcinogenicity in rats, proves that NDMA can cause cancer at any dose. *Id.* at 14-15. But, these arguments do not address the question of

how the Plaintiffs' experts reliably extrapolate from the dosage of NDMA administered to animals to the dosage consumed by Plaintiffs via ranitidine. Because the Plaintiffs do not adequately address or explain dose extrapolation, the Plaintiffs fail to meet their burden under *Daubert*. Also, in alternative, the Court has reviewed the record and has not found adequate explanations from the Plaintiffs' experts as to how they account for dose extrapolation.

2. Cancer Diagnosis Extrapolation

In this section, the Court addresses the helpfulness of the Plaintiffs' experts' reliance on findings that NDMA causes one type of cancer in animals to conclude that it causes a different type of cancer in humans.

a. **Parties' Arguments**

The Defendants argue that the Plaintiffs' animal studies do not fit the question of general causation in humans because the "overwhelming majority" of their animal studies observed only liver cancer, and yet the Plaintiffs' experts opine in their reports that NDMA can also cause bladder, esophageal, pancreatic, and stomach cancers. *See* DE 5696 at 21-23. The Plaintiffs argue in response that "direct site to site concordance between tumor formation in animals and humans is not required to come to a causation conclusion." DE 5913 at 13.

Additionally, the Plaintiffs argue that it is misleading to claim that the "overwhelming majority" of animal studies only observed liver tumors. *Id.* The Plaintiffs reason that the liver tumor findings (which were found primarily in rodents) must be interpreted in the context of the differences between rodent and human bioavailability of NDMA. *See id.* at 13-14. The Plaintiffs explain that the rodent studies primarily observed liver tumors because a higher percentage of NDMA is metabolized in rodent livers than in the livers of larger animals, meaning more NDMA enters the blood circulation of larger animals. The Plaintiffs claim that, for this reason, NDMA is

able to activate tumor formation in a greater number of human organs than rodent organs, and as a result it is misleading to highlight how the studies only observed liver tumors. *Id.*

b. **Analysis**

Animal studies cannot satisfy the fit requirement where they are "too dissimilar to the facts presented in [the] litigation." *See Hollander v. Sandoz Pharms. Corp.*, 95 F. Supp. 2d 1230, 1238 (W.D. Okla. 2000), *aff'd in part and remanded*, 289 F.3d 1193 (10th Cir. 2002). In *Joiner*, the plaintiff relied on studies of mice to prove that PCBs could cause small-cell lung cancer. 522 U.S. at 144. The Court found the studies to be too dissimilar from the facts of the litigation because the mice developed a different type of cancer from the plaintiff (the mice developed alveologenic adenomas whereas the plaintiff had developed small-cell carcinomas), were infants rather than adults, and had PCBs injected directly into their stomachs at a concentration much higher than what the plaintiff had been exposed to. *Id*. The Court found that the respondent had failed to "explain[] how and why the experts could have extrapolated their opinions from the[] seemingly far-removed animal studies." *Id.* (finding that the district court did not abuse its discretion by rejecting the plaintiff's experts' reliance on animal studies).

The Plaintiffs explain how and why their experts could extrapolate with an anecdotal reference to how their own expert relied on rodent forestomach data in support of his opinion that NDMA causes cancer in the human stomach and esophagus; an assertion that government agencies have relied upon rodent forestomach data in evaluating the risk of esophageal and gastric cancers in humans; and an assertion that the human esophagus and stomach are "histologically related" to the rodent forestomach. *See* DE 5913 at 13. But none of these explanations are sufficient to explain how and why their experts can extrapolate here. These assertions may inform the Court that the cells and tissues of the human esophagus and stomach look similar under a microscope, Nat'l

Cancer Inst., NIH, *Histology*, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/histology (last visited Nov. 29, 2022), and that government agencies have relied upon certain animal studies for preventative purposes. But they do not sufficiently explain the relevant similarities and differences between the rodent forestomach and the human stomach or esophagus or the connection between an observation of tumors in the rodent forestomach and the conclusion that tumors can form in the human stomach and esophagus. And, even if it was a sufficient explanation, it does not justify any of the other incidences of site non-concordance identified by the Defendants. Each extrapolation must be supported by specific reasons why it is valid.

The Plaintiffs' additional response, that their rodent studies primarily observed formation of liver tumors only because rodents metabolize much more NDMA in their livers than humans do, is mere speculation. The Plaintiffs assume that the rodent studies would have shown tumor formation in a greater number of organs if rodents had a bioavailability of NDMA more similar to that of humans. However, this type of unfounded speculation is precisely the type of unscientific reasoning that *Daubert* is meant to keep out of the courtroom. Moreover, the Court rejects this explanation because the Plaintiffs have failed to compare rodent livers to either the rodent or human esophagus, stomach, bladder, or pancreas to support this explanation.

For these reasons, the Plaintiffs do not sufficiently explain how and why they can extrapolate from findings of cancer in animals to conclude that NDMA causes cancer at non-concordant sites in animals or humans. Thus, those studies are not a fit for general causation.

Based on the totality of the evidence, the Plaintiffs' animal data is not a fit, and is therefore not helpful, to the general causation question in this MDL. *See McDowell*, 392 F.3d at 1298-99. The Plaintiffs' animal data is too far removed from the human-based causation question in this MDL. As a result, the analytical gap between the animal data and the causation question is too

great; furthermore, the Plaintiffs' experts' extrapolation from the animal data is grossly lacking (if not non-existent by the Plaintiffs' own admission), for their reliance on the animal data to be reliable. *See Hendrix*, 609 F.3d at 1194. Thus, the Plaintiffs' experts' opinions, to the extent they are based upon animal data, are excluded pursuant to *Daubert*.

B. FDA's Regulatory Risk Assessments

The Plaintiffs' expert, Dr. Panigrahy, relies on the FDA's ADI limit of 96 nanograms of NDMA per day in support of his opinion that ranitidine can cause cancer. The ADI represents the maximum amount of NDMA that the FDA has deemed safe for human consumption every day over the course of a lifetime. Dr. Panigrahy opines that the FDA's ADI of 96 ng of NDMA per day is evidence that NDMA causes cancer under real-world conditions.

The Defendants request that Dr. Panigrahy be precluded from relying on the FDA's ADI limit to opine that ranitidine can cause cancer. Below, the Court first summarizes the parties' arguments. Then, the Court provides its analysis of whether Dr. Panigrahy may rely on the FDA's ADI to opine that ranitidine can cause the Designated Cancers.

1. Parties' Arguments

The Defendants seek to exclude Dr. Panigrahy's opinion that the FDA's ADI limit of 96 ng per day of NDMA is "evidence of real-world cancer causation in humans." Panigrahy Dep. 126-27. To support this request, the Defendants argue that regulatory thresholds are not appropriate for establishing general causation because regulatory agencies employ a lower standard of proof than what is appropriate in tort law. DE 5696 at 26. They state that, "a regulatory agency is ultimately concerned with reducing the risk that a medication *may* cause harm, not whether it actually does." *Id.*

The Plaintiffs respond that the Defendants mischaracterized Dr. Panigrahy's testimony, asserting that he "did not opine that the FDA's 96 nanogram daily limit *established* a 96 nanogram threshold to trigger causation." DE 5913 at 27 (emphasis added). The Plaintiffs state that Dr. Panigrahy's testimony should be characterized as stating that the FDA's ADI limit for NDMA "provides *one piece* of evidence that NDMA causes cancer." *Id.* The Plaintiffs rhetorically ask, "If the FDA knew beyond a doubt that no dose of NDMA would cause cancer, why, then, would it establish a limit?" *Id.* Finally, the Plaintiffs re-emphasize that Dr. Panigrahy bases his opinions on the weight of all of the evidence that he reviewed. *Id.*

2. Analysis

The Eleventh Circuit has cautioned against the "methodological perils of relying" on regulatory thresholds "to establish causation." *Williams*, 889 F.3d at 1246-47. This is because a regulatory agency's risk-benefit analysis "does not directly focus on the question of causation in . . . [a] toxic tort case." *McClain*, 401 F.3d at 1250. In other words, the calculus for setting an ADI for a chemical like NDMA is different than establishing general causation because "regulatory standards often build in considerable cushion in order to account for the most sensitive members of the population and prophylactically protect the public (in other words, they are *protective*), while dose-response calculations aim to identify the exposure levels that actually cause harm (in other words, they are *predictive*)." *Williams*, 889 F.3d at 1247. Likewise, "'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.'" *In re Denture Cream Prods. Liab. Litig.*, 2015 WL 392021, at *29 (quoting *McClain*, 401 F.3d at 1249).

Indeed, the FDA itself has cautioned against using ADI as a "realistic indication of the actual risk" associated with a given drug or chemical.[168] This is, in part, because the 96 ng ADI limit represents a 1 in 100,000 cancer risk (meaning 1 in 100,000 persons *could* develop cancer) when exposed to 96 ng *every day for a lifetime*.[169] That threshold—1 in 100,000—unquestionably falls short of the preponderance of the evidence standard required here. The FDA's "risk-utility analysis involves a much lower standard than that which is demanded by a court of law. A regulatory agency such as the FDA may choose to err on the side of caution." *McClain*, 401 F.3d at 1250 (quoting *Rider*, 295 F.3d at 1201).

Relying on FDA thresholds is expressly disfavored by the Eleventh Circuit:

> The FDA's approach differs from [courts'] in another critical aspect. The FDA will remove drugs from the marketplace upon a lesser showing of harm to the public than the preponderance-of-the-evidence or the more-likely-than-not standard used to assess tort liability. "The methodology employed by a government agency 'results from the preventive perspective that the agencies adopt in order to reduce public exposure to harmful substances . . . .'"

Id. (quoting *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 991 (8th Cir. 2001)); *see also Williams*, 889 F.3d at 1246-47. Because the FDA sets ADI limits and recalls drugs "upon a lesser showing of harm to the public than the preponderance-of-the-evidence or the more-likely-than-not standards used to assess tort liability," the ADI standard is simply incompatible with the standard of proof that the Plaintiffs bear in establishing causation. *Glastetter*, 252 F.3d at 991.

Under Eleventh Circuit case law and the FDA's own pronouncement in establishing an ADI, Dr. Panigrahy is precluded from opining that the FDA's ADI limit of 96 ng/day of NDMA is evidence that the NDMA in ranitidine can cause any of the Designated Cancers in this litigation.

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[168] U.S. Dep't of Health & Hum. Servs., FDA, Ctr. for Drug Evaluation & Rsch., Ctr. for Biologics Evaluation & Rsch., *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* 5-6 (2018).

[169] *Id.* A "lifetime" in this context is 70 years.

C. Conclusion on Plaintiffs' Secondary Evidence and Overall *Daubert* Conclusions

For all of the foregoing reasons, the Brand Defendants' Motion to Exclude Remaining Expert Opinions Relating to General Causation and Incorporated Memorandum of Law [DE 5696; DE 5735] is granted. This ruling on the Plaintiffs' secondary evidence reinforces and supports the Court's prior ruling excluding all of the Plaintiffs' primary evidence. *See supra* Section VI. As the Court has now granted all of the Defendants' *Daubert* Motions, the Court turns to the Defendants' Summary Judgment Motion.

VIII. Summary Judgment

Federal Rule of Civil Procedure 56 requires a court to grant summary judgment for a moving party when the party proves that there is no genuine dispute of material fact and that the party is entitled to judgment as a matter of law. In a products liability MDL, the plaintiff must have admissible primary evidence with which to establish general causation. *See Chapman*, 766 F.3d at 1308, 1316. As a result, if the plaintiff does not have this evidence, then there is no genuine dispute of material fact, and the defendant is entitled to judgment as a matter of law.[170]

[170] The Plaintiffs conceded on the record that the Court should grant summary judgment for the Defendants if the Court granted all of the Defendants' *Daubert* motions. Defendants' Sept. 22 *Daubert* Hearing Tr. 195-98.

Here, as explained in this Order, the Plaintiffs fail to produce admissible primary evidence of general causation. Accordingly, it is hereby **ORDERED AND ADJUDGED** that:

1. The Defendants' *Daubert* Motions on general causation [DE 5699, 5698, 5696, 5736, 5732, 5735][171] are **GRANTED**.

2. The Defendants' Motion for Summary Judgment [DE 5734, 5697] is **GRANTED**.

3. The Brand Defendants' miscellaneous expert-related motions [DE 5693, 5694, 5733, 5460, 5856, 5916] are **DENIED AS MOOT**.

4. The Plaintiffs' *Daubert* Motions to strike the Defendants' general causation experts [DE 5841, 5839, 5838, 5868, 5869, 5870, 5900, 5901] are **DENIED WITHOUT PREJUDICE AS MOOT**.

DONE and ORDERED in Chambers at West Palm Beach, Florida, this 6th day of December, 2022.

ROBIN L. ROSENBERG
UNITED STATES DISTRICT JUDGE

Copies furnished to Counsel of Record

[171] The Court references many docket entry numbers in its ruling because the parties filed multiple versions of their motions on the case docket—some under seal and some available for viewing by the public. The titles of the various motions are set forth in the Court's appendix to this Order.

Appendix

***Daubert* and Summary Judgment Briefing**			
Date	**Filer**	**Motion**	**DE**
June 13, 2022	Defendants	sealed Brand Defendants' Motion to Exclude Plaintiffs' General Causation Experts' Opinions Related to Epidemiology and Incorporated Memorandum of Law	DE 5699
June 13, 2022	Defendants	sealed Brand Defendants' Expedited Motion to Strike Plaintiffs' Expert Ramin (Ron) Najafi, PH.D.	DE 5694
June 13, 2022	Defendants	Brand Defendants' Expedited Motion to Strike Plaintiffs' Expert Ramin (Ron) Najafi, PH.D.	DE 5693
June 13, 2022	Defendants	sealed Brand Defendants' Motion to Exclude Opinions and Testimony of Plaintiffs' Experts, Ramin Najafi, Ph.D., Charles Davis, Ph.D. and Other Experts who Rely on Their Opinion	DE 5698
June 13, 2022	Defendants	sealed Brand Defendants' Motion to Exclude Remaining Expert Opinions Relating to General Causation and Incorporated Memorandum of Law	DE 5696
June 23, 2022	Defendants	Brand Defendants' Motion to Exclude Plaintiffs' General Causation Experts' Opinions Related to Epidemiology and Incorporated Memorandum of Law	DE 5736
June 23, 2022	Defendants	Brand Defendants' Expedited Motion to Strike Plaintiffs' Expert Ramin (Ron) Najafi, PH.D.	DE 5733
June 23, 2022	Defendants	Brand Defendants' Motion to Exclude Opinions and Testimony of Plaintiffs' Experts, Ramin Najafi, Ph.D., Charles Davis, Ph.D. and Other Experts who Rely on Their Opinions	DE 5732
June 23, 2022	Defendants	Brand Defendants' Motion to Exclude Remaining Expert Opinions Relating to General Causation and Incorporated Memorandum of Law	DE 5735
June 27, 2022	Plaintiffs	sealed Plaintiffs' Opposition to Brand Defendants' Expedited Motion to Strike Plaintiffs' Expert Ramin (Ron) Najafi, PH.D.	DE 5750
June 27, 2022	Plaintiffs	Plaintiffs' Opposition to Brand Defendants' Expedited Motion to Strike Plaintiffs' Expert Ramin (Ron) Najafi, PH.D.	DE 5751
August 1, 2022	Plaintiffs	sealed Plaintiffs' Opposition to Brand Defendants' Motion to Exclude Plaintiffs' General Causation Experts' Opinions Related to Epidemiology	DE 5915
August 1, 2022	Plaintiffs	sealed Plaintiffs' Opposition to Brand Defendants' Motion to Exclude Plaintiffs' Experts, Ramin Najafi, Ph.D., Charles Davis, Ph.D. and Other Experts who Rely on Their Opinions	DE 5914

August 1, 2022	Plaintiffs	sealed Plaintiffs' Opposition to Brand Defendants' Motion to Exclude Remaining Expert Opinions Relating to General Causation	DE 5913
July 5, 2022	Defendants	sealed Brand Defendants' Reply in Support of Expedited Motion to Strike Plaintiffs' Expert Ramin (Ron) Najafi, PH.D.	DE 5830
July 18, 2022	Defendants	Brand Defendants' Reply in Support of Expedited Motion to Strike Plaintiffs' Expert Ramin (Ron) Najafi, Ph.D.	DE 5871
August 22, 2022	Defendants	sealed Brand Defendants' Reply in Support of Their Motion to Exclude Plaintiffs' Experts' Opinions Related to Epidemiology	DE 5958
August 22, 2022	Defendants	Defendants' Reply in Support of Motion to Exclude Opinions and Testimony of Plaintiffs' Experts, Ramin Najafi, Ph.D., Charles Davis, Ph.D. and Other Experts who Rely on Their Opinions	DE 5956
August 22, 2022	Defendants	sealed Brand Defendants' Reply in Support of Their Motion to Exclude Remaining Expert Opinions Relating to General Causation	DE 5960
September 13, 2022	Defendants	Defendants' Reply in Support of Motion to Exclude Opinions and Testimony of Plaintiffs' Experts, Ramin Najafi, Ph.D., Charles Davis, Ph.D. and Other Experts who Rely on Their Opinions	DE 6005
September 26, 2022	Defendants	Brand Defendants' Reply in Support of Their Motion to Exclude Plaintiffs' Experts' Opinions Related to Epidemiology	DE 6032
September 26, 2022	Defendants	Brand Defendants' Reply in Support of Their Motion to Exclude Remaining Expert Opinions Relating to General Causation	DE 6029
April 5, 2022	Defendants	Brand Defendants' Expedited Motion to Strike Rebuttal Expert Report by Mira M. Hidajat, PhD and Motion for Approval of Expedited Briefing Schedule	DE 5460
April 12, 2022	Plaintiffs	Plaintiffs' Opposition to Brand Defendants' Expedited Motion to Strike Expert Report by Mira M. Hidajat, PhD.	DE 5470
April 15, 2022	Defendants	Reply in Support of Brand Defendants' Expedited Motion to Strike Expert Report by Mira M. Hidajat, PhD.	DE 5483
July 13, 2022	Defendants	sealed Brand Defendants' Motion for Leave to Substitute Expert Witness	DE 5856
August 2, 2022	Defendants	Brand Defendants' Motion for Leave to Substitute Expert Witness	DE 5916
August 3, 2022	Plaintiffs	sealed Plaintiffs' Opposition to Brand Defendants' Motion for Leave to Substitute Expert Witness	DE 5920

August 10, 2022	Defendants	Defendants' Reply to MDL Plaintiffs' Response to Defendants' Motion to Substitute Expert Witness	DE 5934
July 6, 2022	Plaintiffs	sealed Plaintiffs' Motion to Exclude Defendants' Putative Expert Opinions on General Causation Under Rule 702	DE 5841
July 6, 2022	Plaintiffs	sealed Plaintiffs' Motion to Exclude Testimony of Dr. Robert Gibbons	DE 5839
July 6, 2022	Plaintiffs	sealed Plaintiffs' Motion to Exclude Inadmissible Opinions of Dr. Bernard Olsen	DE 5838
July 18, 2022	Plaintiffs	Plaintiffs' Motion to Exclude Defendants' Putative Expert Opinions on General Causation Under Rule 702	DE 5868
July 18, 2022	Plaintiffs	Plaintiffs' Motion to Exclude Testimony of Dr. Robert Gibbon	DE 5869
July 18, 2022	Plaintiffs	Plaintiffs' Motion to Exclude Inadmissible Opinions of Dr. Bernard Olsen	DE 5870
August 24, 2022	Defendants	sealed Brand Defendants' Opposition to Plaintiffs' Motion to Exclude Defendants' Experts on General Causation Under Rule 702	DE 5968
August 24, 2022	Defendants	sealed Brand Defendants' Opposition to Motion to Exclude Testimony of Dr. Robert Gibbons	DE 5967
August 24, 2022	Defendants	sealed Brand Defendants' Response in Opposition to Plaintiffs' Motion to Exclude Inadmissible Opinions of Dr. Bernard Olsen (DE 5870)	DE 5966
September 26, 2022	Defendants	Brand Defendants' Opposition to Motion to Exclude Testimony of Dr. Robert Gibbons	DE 6031
September 26, 2022	Defendants	Brand Defendants' Response in Opposition to Plaintiffs' Motion to Exclude Inadmissible Opinions of Dr. Bernard Olsen (DE 5870)	DE 6034
September 14, 2022	Plaintiffs	sealed Plaintiffs' Reply in Support of Their Motion to Exclude Defendants' Putative Expert Opinions on General Causation Under Rule 702	DE 6011
September 14, 2022	Plaintiffs	sealed Plaintiffs' Reply in Support of Motion to Exclude Testimony of Dr. Robert Gibbons	DE 6009
September 14, 2022	Plaintiffs	sealed Plaintiffs' Reply in Support of Motion to Exclude Inadmissible Opinions of Dr. Bernard Olsen	DE 6010
July 28, 2022	Plaintiffs	sealed MDL Plaintiffs' Motion to Strike Untimely Supplemental Report of Dr. Guengerich	DE 5900
July 28, 2022	Plaintiffs	MDL Plaintiffs' Motion to Strike Untimely Supplemental Report of Dr. Guengerich	DE 5901
August 11, 2022	Defendants	sealed Defendants' Opposition to MDL Plaintiffs' Motion to Strike the Supplemental Report of Dr. Guengerich	DE 5937
August 23, 2022	Plaintiffs	sealed MDL Plaintiffs' Reply in Support of Motion to Strike the Supplemental Report of Doctor Guengerich	DE 5964
June 13, 2022	Defendants	sealed Brand Defendants' Roadmap Brief in Support of Their Motions to Exclude Plaintiffs'	DE 5697

		General Causation Experts and for Summary Judgment	
June 23, 2022	Defendants	Brand Defendants' Roadmap Brief in Support of Their Motions to Exclude Plaintiffs' General Causation Experts and for Summary Judgment	DE 5734
August 1, 2022	Plaintiffs	sealed Plaintiffs' Opposition to Brand Defendants' Motion for Summary Judgment	DE 5911
August 22, 2022	Defendants	sealed Brand Defendants' Reply in Support of its Roadmap Brief in Support of Their Motions to Exclude Plaintiffs' General Causation Experts and for Summary Judgment	DE 5957
September 26, 2022	Defendants	Brand Defendants' Reply in Support of its Roadmap Brief in Support of Their Motions to Exclude Plaintiffs' General Causation Experts and for Summary Judgment	DE 6030