UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA
WEST PALM BEACH DIVISION

CASE NO. 20-md-02924-ROSENBERG

**IN RE: ZANTAC (RANITIDINE) PRODUCTS LIABILITY LITIGATION.**

West Palm Beach, FL
September 21, 2022

DAUBERT HEARING (in person and through Zoom)
BEFORE THE HONORABLE ROBIN L. ROSENBERG
UNITED STATES DISTRICT JUDGE

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*THE COURT:* Good morning, everyone, you may be seated. Thank you. Can you hear me?

Okay, good morning, everyone. We are here in the matter of 20-md-02924, In Re Zantac (Ranitidine) Products Liability Litigation. It is nice to see everybody here in person and also by Zoom.

We have approximately 50 attorneys in person, including all attorneys who will be presenting the motions. We also have attorneys and parties who are appearing by Zoom.

I would like to go through a few administrative matters first. For attorneys who are representing, please come to the podium when you make your presentations, please speak slowly and into the microphone so everyone can hear you, and so Pauline can make her usual perfect record of the proceedings.

For those of you on Zoom, please keep your audio and video off at all times in consideration of the presenters here in court. Everyone in the courtroom should keep masks on unless you are speaking. Please turn your cell phones off. There can be no use of cell phones during the hearing, and no one is to record the proceedings.

This is a big day, indeed, the parties have been waiting and preparing for this day for some while. Back on June 18, 2020, just over two years ago, I entered PTO 30 which included a case management schedule. Within that schedule the parties had agreed and I ordered that all of the Daubert

motions would be fully briefed and ripe by April 21, 2022. On November 15, 2021, I entered a second amended PTO 65, which, among other things, extended the date by which the Daubert motions would be fully briefed until August 22, 2022. So, all of the Daubert motions, Defendants' and Plaintiffs', have been ripe now for about one month.

We have scheduled hearings for today and tomorrow for the Defendants' motions, and September 30th for the Plaintiffs' motions. The attorneys will make the presentations, they have not requested that any expert witnesses be present at the hearings.

The motion that will be presented today is Docket Entry 5699, the brand Defendants' motion to exclude Plaintiffs' general causation experts' opinions related to epidemiology. The Plaintiffs responded at Docket Entry 5915, and the Defendants filed a reply at Docket Entry 5958.

The parties have prepared a schedule for the hearings, with my input, such that they were provided with the time that they requested to make their presentations.

In preparation for the hearings the Court has received and reviewed the briefing on all of the Plaintiffs' and Defendants' motions, approximately 25 primary expert reports from the Defendants' and Plaintiffs' experts, not including the rebuttal reports, approximately 22 deposition transcripts, approximately 40 science studies and reports, and has had the

benefit of two Science Days, one at the inception of the case and one on December 2, 2021.

I have shared with the attorneys some of the general topics that I may be interested in having the attorneys discuss throughout these hearings and they, in turn, have shared with me their PowerPoint presentations which they intend to show here today and over the course of the hearings.

We are on a fairly tight schedule with much ground to cover, so with that, I would like to turn it over now to Defense counsel who will make the first set of presentations during the introduction phase of the hearings.

*MR. CHEFFO:* Good morning, your Honor, thank you. Mark Cheffo for GSK and I, along with Joe Petrosinelli for Pfizer, will be doing the initial presentation here this morning.

Your Honor stole a little bit of my thunder because I was going to thank you and highlight so much of the work that you and your team has done in reviewing all these records and reviewing the documents and asking for things, and it is very much appreciated by both sides.

Also, as your Honor knows, there is just going to be a few of us, probably a relatively few, presenting, but to kind of acknowledge the contributions that I am sure you do know of all of the people who really participated in this effort, so I want to thank them on both sides of our teams.

Your Honor, may it please the Court. Sometimes lawyers have to get up and they have to explain why what they said previously is different, why things have changed, but that is not the case here, your Honor. We told your Honor several things about Ranitidine and about the Ranitidine science from day one, and they remain true now and they were true then.

First, the robust epidemiological data and scientific information and data do not support Plaintiffs' general causation theories with respect to one cancer or five cancers that they have put forward here today. In fact, the information that has been developed should be good news, right? It should be satisfying for people who took Ranitidine, who took the medicine, and may have been led to believe that it can be associated with or cause cancer.

Second, there is no medical institution, there is no scientific organization, there is no Governmental entity that has ever, ever determined that Ranitidine can cause cancer, much less the five cancers that the Plaintiffs proffer in this MDL.

Third, your Honor, we showed your Honor a question.

Next line, please.

This question was important then and is important now in setting the table, we believe respectfully, for your Honor's analysis of the Daubert question here.

Just to go through it because I think there are some

important points that I would like to highlight: Does the scientific evidence reliably demonstrate that Ranitidine use of therapeutic doses of Zantac can cause any of the designated cancers?

When you break this apart, it has to be reliable scientific evidence. We will talk about that. We have to be talking about, which we are here, use of the medicine at therapeutic doses, not kind of petri dishes, real world use of actual Zantac with respect to the specific cancers here, your Honor.

And this is why your Honor's role is so critically important as a gatekeeper. Your Honor will recall that there was a Citizens Petition that was filed, and then within if not hours, days, there were claims and lawsuits filed, and there were at first a few, then there were tens, then there were hundreds, and then there were tens of thousands. Initially, the claims were that this -- Zantac essentially caused cancer in virtually every body system. Essentially, it was a cancer pill. Then what happened?

Then the data started to be developed, scientists continued to do their work, and as the science was published, it wasn't dozens of cancers. The Plaintiffs said, well, it's ten cancers. Then they said, well, it is not ten, it is actually eight cancers. No, no, it's not eight, actually we are going to focus on five. And along the way, as your Honor

knows, tens, hundreds of thousands of claimants were essentially put into the registry and cases were filed.

Next slide, please.

One of the Plaintiffs' experts who you will hear about a fair amount today, this is about two years now when their -- two years after the MDL was established, said she essentially looked at all of the data, and the evidence for the ten cancers was not sufficient to support an opinion that the use of Ranitidine can cause breast, prostate, kidney, lung, or colorectal. So, of course, we don't take any issue with that. We agree with that. Right?

Here is the thing, your Honor: The same body of evidence, the same scientific data that led Dr. McTiernan to form that conclusion, and led literally over a hundred thousand of these claims to exit the registry, is essentially the same data that answers the question here today with respect to the other five cancers.

Next slide, please.

So, this is a quick road map, if you will, of what I intend to cover today. First we'll talk about the scientists and regulators, how they assessed Ranitidine use and cancer risk using reliable methods. Then we will talk about how we believe the Plaintiffs' experts departed from reliable methodology.

Just as a footnote here, this entire hearing, at least

from our perspective, is about methodology, right. To the extent that these are issues that we are talking about, we believe they are Daubert issues, these are not weight issues, these are not cross-examination issues. And then we will talk specifically about the Plaintiffs' forest plots that they put forward which we do not believe accurately portray the state of the science and the take-aways from the science.

Next slide, please.

And your Honor, what happened -- we talked a little bit about the Citizens Petition, so the Citizens Petition was filed, and people didn't just ignore it. It was a serious claim. We had a widely-used medicine and we had claims that it caused a serious disease, cancer.

The scientific community, institutions, you can see these are some of kind of household names, if you will, in terms of the types of institutions, not just in the United States, not just Florida, not just New York, literally all over the world, Asia, Europe, and elsewhere, and they basically got together and they embarked on a mission to answer the question of whether Zantac, right, Zantac can cause cancer amongst the people who actually used it.

Next slide.

And this is a snapshot really to make the point that sometimes we have nameless, faceless institutions, but these are real people, they are not lawyers. They are people who

dedicate their life to public service and to public health. They thought this was an important question and it was a question that they wanted to answer.

Here is the thing: Just like we, as lawyers, and virtually every profession have rules of the road, folks who do this have rules of the road. They have guideposts. It is not a willy-nilly exercise about how are we going to determine whether there is causation or not. What they did and what typically is done, first, when the question is not answered, you say, can we design a study?

Let me make one important point here. At the time that this all occurred, they didn't say -- no one said the question has been answered, right. We can look at occupational data, we can look at dietary NDMA data and we have the answer. No one said that.

Nor did they say the way to understand this question is to do more studies of occupational data or more studies of dietary, right. They didn't do that either.

What they did was, they said, let's follow the rules of the road, you design a study, you try to address chance, bias, confounding. You then conduct a study, and if you believe that it was done appropriately, you submit that study for publication. Of course, that is not the end of the road. Then, of course, the peer review process kicks in, and if it is accepted, you publish.

As you will see in a minute, that happened 11 times with these 25 institutions, and the point of all this exercise is really to see if there is an association. And I know your Honor has dug deep into this, so I am not going to go into too much about Bradford-Hill, but you want to find out if there is an association. Then, if there is an association, is it a strong association, and only if it is a strong association do we then move on to Bradford-Hill. That is the process that happened here.

Next slide.

As I noted, this is from Yoon, but basically all of the experts said the same thing. They said, the way to answer this question is to develop pharmacoepidemiologic studies, that is what is needed to assess causation.

Next slide, please.

They were very thoughtful about this because, again, an important issue, they were going to take a lot of time and effort and initiative here, and they said, what we need to do is develop comparative studies. The way I think about this is really to have an apples to apples comparison and they say it better than I would, which is, the clinical indications of Ranitidine and other H2RAs are almost identical and a control group using a similar indication drug is more appropriate than the general population.

Just as an example, if you want to find out if a

headache medicine is causing some kind of adverse event or problem, you want to look at people who are taking other medicines or who have headaches, so you are not going to get all this confounding, apples to apples. This is not a novel theory, this is what all of these experts say, active comparator is the way to look at this if you want the most accurate, reliable data, and virtually all of these independent experts say that.

Next slide.

And it is not just, you know, Cheffo or Defendants on this, it is the experts, it's the FDA: It's ideal to use an active comparator group taking a drug used to treat the same disease. This is not kind of a novel new concept.

Next slide, please.

And they went about this process. Let me give a footnote here. I think there may have been a mistake in the briefing, I think it may have said that there were 7 million Ranitidine patients. That was in error and I apologize for that. We are clarifying, their study included over 7 million people, but here is the point.

Next slide.

It was almost a million, so yes, it wasn't 7 million, but it was almost a million folks who specifically used Ranitidine. That is a massive number of study participants.

Next slide.

And, you know, we have heard and will likely hear about, well, if someone had medicine that they received from -- they live in a hot state, or it was delivered through a truck that may have been heated, or they left it in their glove compartment, or maybe they used it when it was in their medicine cabinet; we will also hear things about, well, maybe there was some type of endogenous formation, it formed in the body, which, obviously, we all disagree with.

But here is the point about epidemiology. That is kind of why we do it, because you're capturing these real world people. So, if one of those 963,000 people stored their medicine in the glove box or in their medicine cabinet, they are captured within the epidemiology. That is the beauty of these epidemiologic studies.

Next slide, please.

You have heard and you will likely also hear about this kind of latency issue, well, cancer takes a long time. If you look at all the letters after the folks who did these studies, the Ph.Ds, the MDs, I think they know that cancer can take a long time, and they designed this study with that knowledge.

Now, no one suggests every study is perfect, but they did understand that, they did look at this issue, because we all know that it can take a long time. As you see -- and the Plaintiffs may quibble about a year or two here or there, but

the point is that these studies looked at 23 years, nine years, ten years, 18 years. These were long-term followup. Does it mean every single individual was followed up? No. But it was a concept that was on their radar, and they did investigate it.

Next slide.

And this is also important, your Honor, because I think this sets the table. Around the same time that all of this was developing, first, the EMA did not come out initially and talk about Ranitidine, but they did understand the question of -- your Honor knows the EMA is kind of the FDA analog. They had some questions about nitrosamines which means in medicines in general. They also said, we are looking at all the data and we don't have an answer. We don't think that dietary NDMA data answers the question or occupational. There are a lot of different reasons, as they say, so we think that we need to do additional studies. It wasn't mission accomplished at that point.

Next slide.

A few months later they say epidemiologic studies to assess the association between intake of nitrosamine contaminated drugs and risks are desirable, but their conduct is challenging. They basically say here is the way we think you should be thinking about this, scientific community.

Next slide.

And then in September 2020, what we have is kind of

their, you know, list, if you will, their best practices, their concepts of what you should do in order to answer the question. You know what, your Honor, the things I just talked about, about all the epidemiologists in the world's scientific community, it is exactly what they did kind of independently. This all coalesced. This was how the scientific community and world's medical organizations decided the best way to answer this question, and that is what happened.

Next slide.

The medical community did answer this question, and they did speak and they spoke really loudly. What did they conclude?

Next slide.

No associations.

Next slide.

No evidence that Ranitidine is associated with an increased risk.

Next slide.

No compelling evidence that Ranitidine increased the risk of GI cancers.

Next slide.

No evidence that exposure to NDMA through Ranitidine increases the risk of cancer.

Next slide.

Ranitidine was not associated with overall cancer

risk.

Next.

Ranitidine did not significantly increase the risk -- the incidence of gastric cancer.

Next.

Ranitidine was not associated with an increased odds of developing GI malignancies.

Next.

No demonstrable association between Ranitidine use and future gastric cancer.

Next.

The association between Ranitidine and pancreatic cancer is yet to be determined.

Next.

We did not observe any consistent or substantial increase in the risk of bladder cancer.

Next.

Cardwell determined no association, they did find an association with H2RAs, not with -- no association with H2RAs, but they did with PPI, and their conclusion was that further studies are necessary.

That is a pretty loud unambiguous chorus of the scientific community.

Next slide, please.

It wasn't just these institutions or the EMA, it was

also the FDA that looked at this data and said no consistent signals emerged across studies, and studies with comparison to active controls found no association between Ranitidine and overall or specific cancer risk.

Again, these are not equivocal statements.

Next slide.

And they are not alone, right. Basically, this is just a snapshot, we probably could fill many other slides, but the point here is that no institution, no organization, people who devote their lives to public health, to cancer, to safety are not out there saying that Ranitidine causes any cancer. The only people who are saying that are Plaintiffs' retained experts, and my friends on the other side of the V. They stand alone in this, your Honor.

Next slide.

As I said earlier, and we will talk about, this is a gatekeeper function, your Honor. This is a Daubert issue because when you have -- as the Supreme Court has told us, widespread acceptance can be an important factor in ruling particular evidence admissible and a known technique which has been able to attract only minimal support within the community may properly be viewed with skepticism.

You will likely see throughout this, well, I followed the right rules, I read the data, I considered it, but that is not enough here. If I said to your Honor I could add three

things together, two plus two plus two, that is five, my conclusion is going to be viewed with skepticism because just saying I followed a method is not enough.

When you have this world's chorus saying we did this process, this accepted process, and we have come to this finding, you have to view with skepticism, respectfully, folks who divert from those methodologies and from those conclusions.

Next slide.

So, now we are going to talk about how we believe and hopefully show your Honor how we believe the Plaintiffs' experts departed from these rules of the road, right, these reliable methodologies that scientists outside of the courtroom use.

Next slide, please.

So, this is kind of a methodological deficiency wheel, if you will, and the first one we will talk about is the focus on NDMA and dietary and occupational studies.

Next slide, please. Next.

So there is -- your Honor has read the reports, you have read the data, you have read the depositions. There is no nuance here, the Plaintiffs are all in on NDMA. They don't want to talk as much about Ranitidine comparative study data, but from the first page of their epidemiological brief opposition they say all NDMA can cause cancer and all Ranitidine degrades into NDMA. Full stop. Therefore, we don't

need to go any further, let's just get to specific causation.

Next slide.

Here is the problem with that. As I said, no one outside the courtroom, right, the FDA, the EMA, all these experts didn't say we have the answer, let's just look at this. No one did that. No one even said you can do that, no one suggested these questions can be answered by those types of studies. So, again, that should be enough to end this inquiry, but there is more.

These dietary studies, many of them, as you will hear from Mr. Brown a little bit later -- I think it is later -- didn't measure NDMA specifically. These are also based on questionnaires. So, no one is suggesting that these have no use, but they are not what is generally accepted as use for general causation analysis. Asking someone who, unfortunately, had been diagnosed with cancer what you ate 15 years ago, that is essentially what these do.

These have well-recognized limitations, recall bias, measurement imprecision, how things are prepared, and I think a compelling fact here is that in other litigation Dr. McTiernan said, nah, I am not going to rely on this stuff.

Next slide.

Presumably, when these didn't support the hypothesis there, Dr. McTiernan, in another MDL, said, no, you can't ask somebody what they have eaten in the past, yet this is kind of

a marquis argument with the Plaintiffs and their experts in this litigation.

Next slide, please.

Your Honor knows this, the Plaintiffs have also focused significantly on occupational, largely one study, the Hidajat study. We have the same kind of analysis here. No one said mission accomplished. No one suggested you can even use these to answer the question of Ranitidine use. They rely largely, as I said, on the Hidajat study.

What is important about that, too, only ten percent of the data that was used is actual data. A lot of it was inference extrapolation. Of course, these are rubber worker studies, right, people who work around chemicals all day long, inhaling different constituents. It is not an NDMA study about people who actually used Zantac.

Equally important, next slide, Dr. Hidajat told us under oath -- to her credit, she was candid -- these studies were not designed to find out questions about people who actually used Ranitidine; these were studies on rubber workers for NDMA. Of course, that has utility, but it doesn't answer the question here before your Honor.

Next slide.

And there likely will be some back and forth, and your Honor has asked some questions about this, but I think quite clearly the case law clearly also supports this concept, too,

right, that if you want to understand whether a particular product or compound caused a problem, you look at the compound, and then the person, of course to the extent that information is available.

Your Honor knows the first example is the gasoline and Benzene. There the experts were excluded because they looked at Benzene data as opposed to looking at Benzene in gasoline. Again, that is on all fours here, right. Do we look at NDMA data or do we look at Ranitidine data?

If the Plaintiffs are right that the Ranitidine contained NDMA, then we are going to understand how that NDMA functioned and to the extent it caused injury, and again, that is what was done here.

Next slide.

The Burst case also basically excluded the experts for focusing on just Benzene data. There were other reasons, too, that wasn't the only reason, but not focusing on the gasoline data.

Next slide.

And your Honor is, again, likely familiar with the litigation as well there, similar concept. The claim was that zinc in Fixodent caused a certain significant disease end point. The Plaintiffs' expert said, let's study zinc, right, then we can kind of extrapolate into Fixodent. The Courts have said, no, you need to look at Fixodent data based on that.

That is the take-away here. The Plaintiffs in their papers and we'll likely hear, well, the zinc was different, maybe the gasoline and the Benzene was different here, but that is kind of slicing the onion a little too thin. The point here is that you don't look at component data and then try and import it and extrapolate. The Courts have clearly said, if you have data available, like we do here, if you want to understand whether Ranitidine caused cancer you look at Ranitidine in humans. That is what the experts outside the courtroom have done and that is what the case law says.

Next slide, please.

As your Honor well knows, you have asked about this, the experts failed to demonstrate the primary methods for proving zinc in Fixodent causes myelopathy and they were excluded.

Next slide.

I have talked a little bit about active comparators, but let me just say this as well. Kind of another example would be if you have an underlying disease that can actually cause problems, let's say diabetes, people who have diabetes might be at higher risk for heart attack or things like that, and the active comparators here, they account for those issues.

So, if you want to figure out if a diabetes medicine is causing an increased risk of heart disease, you would want to study people who have diabetes, because if you study people

who weren't at an increased risk it would lead to confounded results.

That is the situation here. People who are taking acid suppressant medicines, people who have GERD, those are risk factors for some of the underlying cancers that are at issue here, another reason why active comparators are so important.

Next slide.

Engaging in situational science, Judge Rufe talked about this in the Zoloft MDL. It's basically having one set of rules for a certain set of facts and having another set of rules for kind of a different set of facts or constellations.

Next slide.

And this is what she was talking about, if 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. So two points, it's a methodology issue, and you will also see this throughout the presentations today.

Next slide, please.

The Mirena Court also recognized this. When this happens it raises a red flag that suggests motivated, result-driven reasoning.

Next slide.

Mr. Petrosinelli is going to talk about dose at some

length, so I will be brief on that point. I will say two or three things.

One, it is, frankly, stunning in a case like this when we are talking about medicines that the Plaintiffs have offered no dose, how long does it take, what dose, what is -- the latency issue. None of those questions were offered.

It is so important, again, as Mr. Petrosinelli will talk about, because not every substance that is either good or bad for us causes disease. Our body is kind of an amazing mechanism in the sense that there are certain thresholds. Whether it's radiation, whether it's lead, whether it's arsenic, whether it's X, Y, or healthy things like water, there are certain thresholds. There is almost never a zero sum game, and that is why the dose question is so important here as we go through these hearings.

Next slide.

The Plaintiffs also rely on non-replicated inconsistent findings.

Next slide.

The manual tells us the importance of the need to replicate research findings across science, particularly here, and also consistency. So, we don't want to have just a certain finding, because we all know if you run a certain number of tests in any study the likelihood of getting one finding from chance is pretty high, so you need consistency. You need to

look at it and say, is there consistent results. You also need to have replication and you need to have statistical significance, as we will talk about.

Next slide.

And then there is the concept of cherry picking data. Your Honor certainly knows what that is, and I think we will have some examples of that.

Next slide.

This highlights really a more broad point. I think I have seen some commentary from Plaintiffs that the Court's role is limited, and of course it is not open ended, there is a limit to this, but it doesn't mean that it should be not focused on the data.

What the Joiner Court has told us and its progeny is that your Honor is supposed to do, which is what you have, in order to understand if there is cherry picking in the data, if the science doesn't make sense on a granular level, that is certainly within your purview. That is something that the Supreme Court and others have expected Courts like your Honor to be doing.

Next slide.

Now we will talk about the forest plots. I know that is probably the most exciting part of your morning, so I will jump right into it.

Next slide, please.

This is a refresher, really briefly, just for those of us who don't spend eight hours a day staring at forest plots. The way scientists kind of plot data, record data is on these forest plots, and that's what this is. It looks like a T, right. These are four kind of exemplar end points.

The first end point, what does it show? It shows a non-statistically significant finding. How do we know that? We know that because if the horizontal axis either crosses or touches that vertical axis, that means it is not statistically significant on either side, right. Then we have on the right side of the box an increased risk, on the left side is a decreased risk.

So we have the first one is not statistically significant increased risk. The second is not statistically significant decreased risk.

That brings us to end point number three. As you can see, this is a statistically significant finding in the increased risk category, but there is something that is notable about it. You see that the line is long, or at least longer than the others, and that typically represents that there are fewer people in the study, so the reliability speaks to that line.

And then the final point is a statistically significant negative finding with a higher level of confidence, if you will.

If we were looking at these, or more importantly, if scientists outside the courtroom were looking at these, for example, they would say a few things. One, they would say there is no consistency. We have negatives, we have positives, we have not statistically significant, and they would also certainly say there is no replication. Someone couldn't look at end point four and say, ah-ha, this is protective. Nor could they look at end point number three and say, ah-ha, this is a problem, this is a negative issue.

With that, your Honor, we are going to start with the bladder. The Plaintiffs seemed to have focused on bladder, and they started with it in their papers, so we will take it head on and jump right in.

Next slide, please.

These are the bladder cancer data.

Next slide.

So, a few points just as a preview. What we will try to do, your Honor, and I will try to explain this so we are all on the same page, but to the extent we cover a particular end point and it shows up in others, we are not going to keep going through the same thing. You will see us graying it out. Gray is our little key for either we have covered it or it doesn't support the Plaintiffs' position, but I will explain that. I just wanted to give a little preview of where I am going.

And this is from the Plaintiffs' papers. This is not

our forest plot, this is theirs. You have seen a lot of them, but the Plaintiffs put this in their brief, and the blue represents the dietary NDMA, not Ranitidine studies, and the red represents the occupational studies.

We have talked at some length about that, we don't think they are reliable, we don't think the scientific community or the FDA or the EMA thinks they are reliable.

Next slide, please.

Those are in gray.

The next category of data points that we are going to talk about -- next slide -- are those that are not statistically significant. You can see they all cross the axis, so they are not statistically significant. Why is that important?

Next slide.

The Sandoz case tells us the burden is on Plaintiffs to show that well-conducted epidemiological studies do show a statistically significant relationship.

Also, I think it is in the briefing, Dr. Salmon conceded this and Dr. Lee also in her deposition, at page 82, it could be 83, testified to this point, that statistical significance is needed for an association.

Next slide.

On top, a little bit of the icing on the cake, not just is the table statistically not significant, the authors

talk about confounding, but even though it is on this slide that the Plaintiffs proffer as supporting general causation, their own expert says the information is not informative on the relationship between Ranitidine use and bladder risk. Not informative, their expert says that.

Next slide.

Then we have these two findings here, Norgaard, we have the crude and the adjusted. I think, as your Honor probably is aware, the crude is really just that. Before the study was published, or during the process, the actual scientist doing it said there is something that is confounded here. The crude is not the most accurate representation, so we are going to adjust it to try to address confounding, which is exactly what they are supposed to do.

So, while the Plaintiffs have put forth the crude number, which is statistically significant and positive, when it is actually adjusted by the study authors, it is not statistically significant and the end point moves to the left.

Next slide.

There is another thing about Norgaard. Red is an indication to you, your Honor, that this was not on the Plaintiffs' initial slide. So, I want to be clear to you that the Plaintiffs were kind of adding a point here.

I think this point is important because the Plaintiffs have and will talk a lot about, well, the studies, they don't

look at latency enough, they don't follow people enough, but there was a study and there was an end point in the Norgaard data where those scientists actually looked at long term ten-year followup and ten plus prescriptions. Now, the Plaintiffs determined not to include it on the slide, but you can see what happens, the end point moves all the way over into the decreased risk factor.

Next slide.

And that is undoubtedly why, when the study authors themselves looked at this data -- they didn't have a dog in this fight other than public health -- they said, looking at all of this and reflecting routine clinical practice, we did not observe any consistent or substantial increase in the risk of bladder cancer in Ranitidine users. They didn't focus on the crude and say, ah-ha, this is the answer. They said, looking at all the data, this does not show an association.

Next slide, please.

Also not statistically significant, right, and no surprise, the study authors say no associations were observed, we found no evidence that exposure to NDMA through Ranitidine increases the risk of cancer. That was their conclusions notwithstanding the fact that it is on the Plaintiffs' chart here as supporting general causation.

Next slide.

This is a truism both in science and certainly in the

law, when an expert relies on the studies of others he must not exceed the limitations the authors themselves place on the study, and there are a few core principles. I can look at the data that these experts generate, then you need to look at at least their conclusions, and the other thing about it is that the conclusions are peer reviewed just like the data. They went through the peer review process as well.

Next slide.

That brings us to the MSK study. First of all, this is a non-published study. Dr. Braunstein, as your Honor knows, was deposed. He was asked kind of squarely flat out, do these results -- can they be used to say that Ranitidine increases the risk of cancer? No, can't do that. Does this provide evidence, any evidence of increased risk, much less causation? He said, no, it doesn't do that, yet it is on the chart.

And equally important -- next slide -- Plaintiffs' expert, Dr. Moorman, says these don't provide useful data. I don't rely on this. This is not something that I credit as part of my methodology.

Next slide, please.

Then we have Cardwell. There are three things, I think, three brief points I would like to make about it.

First, the Plaintiffs use non-comparative data. I have spoken a fair amount about active comparator, but the analog to that or the other side is using general population,

people who are not in that group, so it is not an apples to apples. It's more an apples to oranges. That is the data point that is included here. When you actually look at the H2RA data, you see no statistically significant finding, and also, even if you were to credit this, there is no consistency in replication. We will show that graphically, if you will.

Next slide, please.

The first point is, when it is compared to an active comparator, the H2RA, as I indicated in my opening comments, it is a statistically significant finding, but when the study authors compared it to other H2RAs, which is the class of medicines that Ranitidine is in, you see the finding. It is basically down the middle. That is a significant finding.

Next slide.

So, what does this show us? This is -- particularly when you take away all the things that even the Plaintiffs' experts have said they don't rely on, or things that are just not reliable based on the scientific community, this is a picture of no association, certainly no strong association, and no causation. It is not a picture of consistency or any replication with respect to causation.

Next slide, please.

We are now going to talk about esophageal cancer.

Next slide.

We are able to go through this a little bit quicker.

So, the points in gray are the things I talked about already, but I would like to talk about Habel just once more because -- next slide -- essentially Dr. McTiernan doubled down on this one. This is a similar finding, but she looked specifically at the esophageal findings and said it is not possible to look at the associations between esophagus risk and Ranitidine use with the Habel study. Full stop. Yet it is on their slide as supporting it is statistically significant when their expert says can't -- it is not even possible to look at this association.

Next slide.

The McGwin study, your Honor probably dug deeply or at least into this study, so just a few things about this. This study was based on adverse event reporting. Certainly I am not going to stand up here before the Court and say adverse event reporting is not important, it doesn't have a place, it doesn't have a role, it does. It is a blunt instrument, it is used by pharmaceutical companies, the FDA, and others to signal detection.

The problem here with using it for causation is a few things. One, every time somebody files a lawsuit or a claim that becomes an adverse event, so it massively skews the adverse event. It is not a voluntary type thing a doctor or patient would do, and this study actually captured the point when you would expect to see a massive influx of adverse events

through litigation. So, that is one of the issues.

Next slide, please.

We have a benefit here, notwithstanding the Plaintiffs' slide, of focusing on what their own experts say, and Dr. Moorman said no, it is impossible, impossible to calculate the risk using this type of data.

Next slide, please.

Dr. Moorman we agree with, and she is not alone. The FDA basically again, as I am saying, certainly has a use, certainly has a purpose, but it is a data mining tool, it is not for establishing causation.

Next slide, please.

So, when we look at esophageal cancer and we account for the things that the Plaintiffs' experts have said, and we look at dietary and occupational as unreliable, this again is the picture of no association, no strong association, no causation, no consistency, no replication.

Next slide, please.

We'll turn to stomach cancer, your Honor.

Next slide.

A lot of gray because, we have talked about them, your Honor, so they are either things that the Plaintiffs' experts have disabused us of, dietary or occupational, or things where they are just squarely statistically significant in favor of protection, right.

So that leaves us with Liu, and I want to talk about that. Your Honor may recall, I talked about that at the last Science Day and it's the same data point.

The Plaintiffs have put up a one-year data point showing a statistically significant increase in risk.

Next slide, please.

What is not included on their slide is that the authors did a few things; they looked at people who took the medicine and developed stomach cancer. Remember, it's the Plaintiffs saying there is a long latency period here for cancers. They looked at one year and they saw that first green line, statistically significant. Then they looked at after two years of use, and after three years, and they saw it is not statistically significant, and that end point is shifting to the left. What they basically said is that this suggests reverse causation.

As a quick example -- next slide -- unfortunately, if someone was to have stomach cancer that was undiagnosed, the symptomology of stomach cancer, you might take something like Zantac to help relieve it, then within five months, eight months, 11 months, you may get diagnosed with cancer. What these experts recognized, it is not the fact that you took the Zantac two months ago or three months ago, it is the fact that it wasn't diagnosed, right.

So, that is reverse causation and that is something

that good science tries to account for. Remember, the EMA, as one of their guideposts in on of the early slides I showed the Court, said account for reverse causation, bias. So that is what the study authors -- they didn't say this supports evidence of general causation for stomach cancer.

Next slide, please.

Once again, your Honor, when we account for the grade items and the things the Plaintiffs' experts have distanced themselves from, no association, no strong association, certainly no causation, and there is just no consistency here. This is the poster child for lack of consistency in their application.

Next slide, please.

Liver cancer, we will talk about that briefly.

So, the Kantor study, there are two things about it. You see two end points, the first is statistically significant, that is regular use. That is not the comparator study that we are talking about, that is the apples to oranges, not necessarily the apples to apples. And then you will see when they actually do the active comparator study, what happens? What you would expect to happen, there is no statistical significance, and the end point is almost at the axis.

Next slide, please.

That is why outside the courtroom the experts and scientists who actually did this study, they didn't conclude,

like the Plaintiffs here are saying, or their experts are saying, that this is evidence of causation. They said there is not even an association between the risk of cancer when you look at the active comparator studies.

Next slide.

And again, your Honor, you know probably where I am going to go, to say this is a picture of no association, causation, strong association, consistency, or replication. This is what you would see if -- frankly, this should answer the question, right? That is what we're trying to find, is there an association? So this, like the others, answers that question.

Next slide, please.

And then finally pancreatic cancer.

Next slide, please.

So, we've talked about all the others, you see Adami and Kim are kind of on the negative side, so let's talk about McDowell. I will highlight, it says ever use. That's not an active comparator study.

One quick word on this. This goes to the situational science point, so it is kind of hard to follow it sometimes. Sometimes they say the Ranitidine data is not reliable, you shouldn't look at it at all, but then they rely on Ranitidine data. They say active comparator doesn't really answer the question, you need to look at certain use, but then they will

rely on active comparator, so this is kind of the idea of situational science.

Next slide.

Notwithstanding this finding, the study authors didn't say mission accomplished, we found the answer. They say that the association, not even causation, is yet to be determined.

Next slide.

And why is that? Well, this is another data point that wasn't included on the Plaintiffs' chart, but again the Plaintiffs have said that some of the limitations of these studies is that they don't follow longer term use, or they are not people who use the medicine, but in fact McDowell did look at people with over six prescriptions and that data point was peer reviewed, but not included here.

What did it show? People who actually used it longer have a less incidence and non-statistically significant risk as opposed to the finding that they have included.

Next slide, please.

Again, you can't look at this, I don't think, outside the courtroom and people would say, ah-ha, this shows association, much less strong association or causation. This is the picture of no association, no consistency, and no replication.

Next slide, please.

So, your Honor, before I hand the baton to my friend,

Mr. Petrosinelli, just to kind of recap, the scientific community looked at this issue the way scientists do outside the courtroom, not bound by kind of litigation influences or anything on either side. They looked at it and they used reliable methods. No one has challenged that.

The Plaintiffs' experts, in the face of that data and those data points, essentially had to contort the way that they have approached this, and they know how to do this the right way, as we have pointed out and as you will see. You will see in other situations, when they do this outside the courtroom, they know how science is supposed to work.

Then, as we just went through, when you look at these forest plots, your Honor, it is hard to come to the same conclusion even as a nonscientist that the Plaintiffs are asking the Court and their experts are saying is an appropriate methodology.

Next slide.

The reliable literature does not support an association, certainly not generally accepted that Zantac causes cancer. When people and experts depart so far, so astray from what the rest of the scientific community does, this warrants the Court's clear attention. This focus on NDMA and dietary data are not reliable or relevant. An analysis of -- when you actually dig into the data, it demonstrates the flaws in the Plaintiffs' methodological analysis, which is

really at the heart of what we are here for today and the next few days.

With that, your Honor, I very much appreciate your patience and I will turn it over to Mr. Petrosinelli.

*THE COURT:* All right. Thank you very much.

*MR. PETROSINELLI:* Your Honor, good morning.

*THE COURT:* Good morning.

*MR. PETROSINELLI:* I am going to bring us home with two points that relate to the general causation inquiry here, and that is the question of dose and what the Plaintiffs have offered on dose, and their application of the Bradford-Hill and weight of the evidence methodologies.

Just to jump right in on dose and what I am -- when I say dose, your Honor, I am really talking about two things. There is the question of threshold dose, the dose at which a compound can be hazardous to human beings generally, and then there's dose response relationship, which is a separate concept. I will talk about both of those.

I am going to start with threshold dose because that is easy. The Plaintiffs' experts do not offer any opinion, let alone a reliable opinion, on what is the dose that supposedly, in their opinion, can cause cancer in human beings, or for any of these five cancers, and why didn't they do that?

In their brief they say a couple of things.

One is, they say that is a specific causation

question. That is their main sort of Daubert defense to that point, is that we will talk about dose when we get to specific causation, that is not a general causation issue. That is just entirely wrong under the Eleventh Circuit case law.

Next slide, please.

I think of Chapman and McClain as the two leading cases in the Eleventh Circuit on general causation issues as they relate to toxic tort cases. When you read those opinions, it could not be clearer, these are quotes from the opinions, but just to take McClain, the burden in a toxic tort case, to satisfy it the Plaintiff must, not may, must demonstrate the levels of exposure that are hazardous to human beings generally, that is general causation, as well as the Plaintiffs' actual level of exposure. That would be specific causation.

In the Fixodent case, the Eleventh Circuit opinion in the case, same thing, neither of their general causation experts offered opinions about how much Fixodent must be used for how long.

Next slide, please.

District Courts in the circuit after McClain and Chapman have, of course, applied this methodology. I have here two of Judge Rodgers cases. She would be happy I said it here twice already in my presentation, her two most recent cases assessing general causation in toxic tort cases. The Deepwater

Horizon piece of it that she got from Judge Barbier when the Florida residents made claims couldn't be clearer. The burden on general causation must demonstrate the levels of exposure that are hazardous to human beings generally, and she noted the same in Abilify.

So, the question is, what have the Plaintiffs done and said with respect to that? Let's look at what they have said in their briefing because this statement that they made I thought was quite extraordinary and supremely relevant to what we are talking about.

Next slide, please.

I don't know if your Honor saw this because this is in their motion to exclude the Defense experts, the motion that is being heard next week, but this is what they say. Their general causation theory -- so we ar not talking about specific causation -- in the litigation is for long-term use of Ranitidine. The claim is not, not that Ranitidine causes cancer after one dose or even a year's worth, but over many years of regular use.

That is a pretty extraordinary statement for a couple of reasons.

One is, they have conceded as a general causation matter, meaning we should get summary judgment whatever happens -- and we will talk about this when we get to the summary judgment motions -- that if someone takes Ranitidine

for a year, they are not claiming they have proof, reliable proof or even any proof of general causation.

Now, the second thing that is interesting about the statement is what they are saying from a general causation perspective, they tell us, is it is many years of regular use. That is not a dose, that is not a frequency, that is a description. That is what is missing here.

What they have to tell us is how many years, what is regular use, how many doses, in other words, of the product.

Those are the two components of exposure in a toxic tort case, the quantity of the exposure and the duration of the exposure. This is what McClain and Chapman say must be part of a general causation presentation to be reliable, and they haven't done it. All they have said is many years of regular use.

Let's see what their experts have said.

Next slide.

Dr. McTiernan, no opinion. We asked her point blank on this issue of threshold dose and duration. We first asked her about Ranitidine. I don't have an opinion on that.

Then, because they say, well, the Ranitidine data is not the key data, it is the NDMA data, we said, okay, NDMA. Don't have an opinion on that. You might wonder where the 47 nanograms came from. She had testified that there was a dietary study that showed -- tried to estimated levels of NDMA

and it showed an increased risk with every 47 nanograms, or something like that. And we said, okay, put aside whether that is accurate or not, how long, how long would it take for each of the cancers -- if you ingested 47 nanograms could you say would cause or could cause cancer? Don't have an opinion on it, I can't tell you.

Next slide, please.

Dr. Moorman went the opposite way, she went with the single pill theory. We asked her for both Ranitidine and NDMA, can a single pill of Zantac cause cancer? And her theory is, well, if it is a genotoxic compound, which means it can alter the DNA, then theoretically one pill could do it, any level of exposure could cause cancer, and the same thing with NDMA.

I think the Plaintiffs realize that that is a Daubert loser. Under the case law, McClain is the best case on this, this is what the expert said, any dose could cause it.

Next slide, please.

So, the Plaintiffs back pedaled. I don't know if your Honor saw this, this is a brief filed last week, this is their reply in support of their Daubert motions filed last Wednesday. They say, well, Dr. Moorman is correct that a single molecule could cause cancer because if it is a genotoxin there is no safe dose, but, but, we, the Plaintiffs, are not arguing here as a general causation matter that a single pill or molecule could cause cancer as a legal matter.

When they say as a legal matter, they mean to satisfy Daubert, of course. So, now we are back to square one. They are not saying that any dose could cause cancer, but they won't tell us what the dose is. They say many years of regular use. That does not satisfy McClain and Chapman.

Now, I saw on their slides for today they sort of make two more points. One is, they say the Eleventh Circuit cases say you don't have to give a precise dose. Of course that's true. No one is talking about they have to say it is 150.5 nanograms for 3.7 years. That level of specificity is not what is required, but some numbers are required, that is what the case law says, a range, an estimate, and they don't do it. They won't do it.

They have explicitly disclaimed it for the reasons we talked about, either because they mistakenly thought it was a specific causation question, or they didn't think that they had to provide any more specificity.

That is a fatal defect at the most threshold level, no pun intended, of their Daubert general causation presentation under the case law.

Dose response, separate concept, which is, put aside this question of threshold dose, let's say there was no threshold dose, let's pretend for a moment, or whatever the threshold dose is. At a certain point the concept of dose response is that as the exposure increases, the risk increases

for the outcome, and whether -- the slope of the line depends on how quickly the risk increases.

What does the Eleventh Circuit tell us about that?

Next slide, please.

It tells us something pretty clear. The single most important factor to consider in a toxic tort case when you are dealing with general causation, and we are talking about general causation here -- and I have McClain and Chapman up again and you see in McClain, this is what I mentioned before, their general causation expert said any level is too much and wouldn't give any numbers or any specificity about a dose response relationship, and the Court said not going to be admissible. And of course, in McClain, as you know, they actually reversed a jury verdict in favor of the Plaintiffs on this question.

So, what do the Plaintiff's experts say about dose response relationship?

Next slide, please.

Dr. Moorman can't say anything about it with respect to the Ranitidine studies because their position, as you know, is the Ranitidine studies have these limitations, they don't follow the patients long enough, they don't measure precisely enough the exposure, and so Dr. Moorman says, I cannot tell you what the shape of that dose response line looks like. I can't describe anything about dose response from those studies.

And I think Dr. McTiernan does the same.

The one expert they have who actually does try to tackle dose response is Dr. Salmon, and so you will hear from Mr. Holian in much more detail about that later, but his methodology, the way that he tries to construct a dose response curve for both Ranitidine and NDMA is totally unreliable, unmoored to any science anywhere. That is the one expert they have who tries to do it, but they have to do it, they have to have reliable evidence of a dose response relationship.

Where they tell us -- when I say reliable evidence, where they tell us what number of years increases the risk at what doses, that is the dose response relationship, and that is what the case law says they have to provide as a matter of general causation, the single most important factor, and they don't have it.

So, for those kind of two independent reasons relating to dose, they can't satisfy the general causation.

Let me shift topics to my second topic, which is the application of the Bradford-Hill analyses that were done.

Next slide, please.

We have addressed in the briefs that not all their experts conducted a Bradford-Hill or weight of the evidence or applied either of those methods, but some did.

Next slide, please.

The first thing I want to say about it is emphasize

what Mr. Cheffo mentioned, of course I think this point is not in dispute. You don't even get to a Bradford-Hill analysis unless you have reliable evidence of an association, and for all the reasons Mr. Cheffo described, they don't have any reliable evidence of an association, and therefore you would not get to the question of whether it is causal, which is what Bradford-Hill does.

This is Judge Rodgers' Deepwater Horizon opinion, but there are plenty of opinions that say this. So, what I am addressing now is, let's assume they get past that, even if there were reliable association in the data.

Next slide, please.

So, what does case law tell us? There is a rich body of pharmaceutical MDL case law on the application of the Bradford-Hill method or the weight of the evidence method. The Mirena and Zoloft opinions are probably the leading pharma MDL opinions on this question.

Judge Engelmayer's opinion in Mirena is like a Daubert tour de force, it is an amazing explanation of all the things we have been talking about today, frankly.

What you glean from this are two concepts, and they are kind of separate in my mind. One is that if you are going to apply a Bradford-Hill method, you have to rigorously explain how you weighted the criteria.

In other words, you can't just say, which is what the

Plaintiffs' experts do here, I weighed all of the criteria, I gave appropriate weight to this or that. That doesn't get you past Daubert. You have to rigorously explain how it is that you weighted it.

So, for example, if the association that is seen in the epi studies is weak, you know, it is one point something, which is basically what it is in all of the Ranitidine epi studies, and frankly, most of the NDMA studies, but you are going to conclude causation, you have to say, well, yes, the association was weak, I admit that, but the dose response relationship was so strong, and the consistency was so strong, that those two factors I weighted heavier than the strength of association, something like that.

You don't just say I went through all of the nine factors, I weighed them appropriately, and this is how I came to my judgment.

The second thing is shown in the Zoloft quote, which is, you can't just explain how you weighed them, but there has to be a scientific method of weighting. In other words, you can't say I weighted the strength of association less than these other factors, and so I am done under Daubert, I passed Daubert because I told you how I weighed them.

You have to weigh them in a reliable way. The weighing has to be supported by science, and what you will hear later on when you hear about Dr. McTiernan and Dr. Moorman, you

will see how they addressed and weighted some of these factors and they did things inconsistent with how they did it with their peer review publications, inconsistent with prior testimony, inconsistent with the way that the FDA or the EMA used these factors, inconsistent with the study authors. I'll talk about that in a second. Those are the two things you have to do under Bradford-Hill that are absent here.

Next slide, please.

I thought this would be interesting. I know your Honor knows many of these judges and many of their MDLs. There has been an abundance of pharmaceutical MDLs in the past several years -- I guess Deepwater Horizon is not pharmaceuticals -- these are all products MDLs, but all of them but that one are pharmaceutical ones where these judges -- these are experienced MDL jurists -- tackled the issue of the application of a weight of the evidence or Bradford-Hill approach in assessing general causation, and every single one of these Courts excluded the opinions under Daubert, every single one.

Why is that? I think there is always case specific things. You can never look at one case and say I can now do the same thing because the studies are different and so on, but I think you can glean three things in common that these cases had.

Next slide.

In all of these cases, the scientific community had studied the issue and no one outside of the courtroom had concluded causation, no regulator, no medical organization, no medical college, no peer review literature. No one had concluded causation.

The second thing is that the Plaintiffs experts -- I should say in all of these cases basically, there may be some exceptions, these were highly qualified epidemiologists and other experts on the Plaintiffs' side. In other words, the Defendants didn't challenge qualifications of these experts.

Judge Rodgers, I think, in her Deepwater Horizon opinion says, impeccably qualified experts, and in all of these cases these highly qualified experts purported to apply Bradford-Hill or weight of the evidence, and they concluded causation, notwithstanding no one else had.

The third thing is that the Plaintiffs' experts, in applying the Bradford-Hill factors, they exceeded the conclusions of the authors of the studies on which they relied, the very studies on which they relied. When I say exceeded the conclusions, I don't just mean, your Honor, they concluded causation and the studies didn't, because epidemiologic studies don't often talk in terms of causation.

What they did that was different than the study authors and some of the things you just heard about from Mr. Cheffo, the authors' analyses of their own data and what their

data means, the authors' discussion of how they controlled for confounding or couldn't control for confounding, the analysis within the studies and conclusions the authors reached about their own data, the experts in all of these cases exceeded those conclusions, offered opinions that were inconsistent with those conclusions.

All of these things are present here.

Next slide, please.

I want to talk about in my two minutes -- Mr. Cheffo stole some of my minutes -- Abilify. There are, of course, some cases in which they weren't excluded. Why? Look at Judge Rodgers opinion in Abilify. There was an epidemiologic study of Abilify, the product in question, that showed statistically significant massive increased risks of the diseases in question. Look at the relative risks, five to almost eight, highly statistically significant.

Next slide.

Look what Judge Rodgers said, broad scientific consensus about the existence of an association, the opposite of what we just talked about in the other MDLs. All the regulatory agencies had concluded as much, and the study unchallenged in the literature, totally different than what we have here.

Next slide, please.

And Judge Chhabria in Roundup, I just wanted to point

out the standard he set out which does take into account those for general causation. But look at what Judge Chhabria said, it is a close question, he said that four or five times, and he says, in the Ninth Circuit my perception is that there is more deference to experts in close cases than might be appropriate in some other circuits. What are the other circuits he cites? The third and the Eleventh. If Judge Chhabria were here I think he would say, if I was in the Third or Eleventh Circuit I would have granted this Daubert motion. That is what he is telling us here.

Next slide.

Judge, finally, the Plaintiffs say the human Ranitidine epidemiology leaves the question open. We don't think that is true for the reasons Mr. Cheffo just explained, but let's say it were true. What does that mean for the law? What that means is the Daubert motions have to be granted, that you can't conclude causation, because in the real world, if the human Ranitidine epidemiology left the question open because there wasn't long enough followup and because there wasn't enough information about dose, we know what scientists would say because we saw what scientists did.

They didn't say, as Mr. Cheffo pointed out, oh, we have this 20 years worth of NDMA dietary research, that answers the question. We can fill that gap with that research. What would they do? They would do more studies on Ranitidine. They

would follow these populations for two or three more years and see if the increased risk of cancer that the Plaintiffs say is bound to pop up because you didn't -- that is what they would do.

What they would not do is do what the Plaintiffs have done here and say, then let's look at lesser levels of evidence, the dietary and occupational stuff by analogy.

Next slide, it's my last slide.

That is because law has to lag science. Your Honor has seen this quote, it is in McClain, I think it originated in the Seventh Circuit. This is Judge Seibel's -- she had the first Mirena MDL, there were two, and what does it mean? I like the way that she describes it. It is not that I am saying -- she excluded the experts. It's not that they are insincere, it is not that Dr. McTiernan and Dr. Moorman haven't convinced themselves that there is enough evidence for them to believe there is causation, or it is not that some day it might not be validated -- I don't think so here -- but it is not that, it is that the law can't wait.

You judge the science as it is today, and as it is today, there is no reliable evidence of causation, and that is why our motions fundamentally should be granted.

Thank you, your Honor.

*THE COURT:* Thank you very much.

Okay. You are just over by two minutes. Certainly

the Plaintiffs can have an extra two minutes if they need it.

On our schedule we have a 15 minute break now.

So let's see, it is 10:18, so that means we should return at 10:33, and then we will pick up with the Plaintiffs' presentation and go right into the Defense rebuttal before we break for lunch.

We will be in recess until 10:33. We will see you back then. Thank you.

(Thereupon, a short recess was taken.)

*THE COURT:* Okay. From the Plaintiffs.

*MS. FINKEN:* Good morning, your Honor, Tracy Finken on behalf of Plaintiffs.

*THE COURT:* Good morning.

*MS. FINKEN:* I am going to address certain issues today and then my colleague, Daniel Nigh, will address some other issues when I am finished.

Your Honor, like Mr. Cheffo said, we also told you several things on day one in this case that were true then that are still true today. Many of those things that we told you back then remain undisputed, and I think it is really important, your Honor, that we don't lose sight of the fact that, one, all Ranitidine degrades to form NDMA.

Two, NDMA is a known genotoxic carcinogen, that is not disputed.

Three, Ranitidine has been globally recalled because

it contained NDMA, a known genotoxic carcinogen.

And four, we told you back then, and we are going to show you today as well, that there has been consistency demonstrated across all categories of evidence that the exposure to the NDMA, the genotoxic carcinogen in Ranitidine, can increase the risk of the five cancers that we are alleging in this case.

Mr. Nigh will go into some of the epidemiology and dose responses, but I just wanted to address that up front.

One of the other things, your Honor, that we agree with from Defense's presentation is that there has been an abundance of MDL judges who have tackled the general causation issue similar to this case, however, the difference is, and at a cursory review of those Daubert opinions, not one of those cases has the overwhelming abundance of evidence that we have in this case. And we will go through that in more detail as we go forward.

So, to begin, your Honor, the question is relatively straightforward, the issue is whether the NDMA in Ranitidine is capable of causing the five cancers at issue. Defense counsel admitted that this was the issue in front of this Court in July.

Now, today they seek to reframe the issue so that it only is about Ranitidine and exclude any evidence about NDMA, and they seek to have this Court and Plaintiffs' experts put

blinders on and ignore any evidence regarding NDMA. Your Honor, this simply defies logic.

Make no mistake, this case has always been about the genotoxic carcinogen NDMA. If Ranitidine did not degrade to form NDMA it would still be on the market today, the Defendants would still be making billions of dollars a year on this product, but it is not. It cannot be found in the United States. Every scientific authority and regulatory authority agree in the world, they agree that NDMA is a genotoxic carcinogen. This has been known for more than 50 years, your Honor.

So, under Eleventh Circuit precedent, there are two types of cases when it comes to toxic torts, and I am going to briefly discuss those, and they are outlined in McClain versus Metabolife, which Mr. Petrosinelli talked about in some detail.

So, under Eleventh Circuit precedent, to determine the answer to the question we just posed, the Court needs to look at, one, whether it is generally accepted in the medical and scientific community that NDMA can cause cancer. If the answer to that question is yes, then the case proceeds to case specific causation and extensive Daubert analysis does not need to be undertaken in this stage.

If the Court determines that the answer to that question is no, then the Court must conduct a Daubert analysis of Plaintiffs' experts' general causation opinion.

To frame the question under McClain category one, is it generally accepted in the scientific community that NDMA can cause cancer, and that question is applied without regard to specific dose, and we cite to authority demonstrating that in our brief, specifically the Williams versus International Paper case.

The answer to the question whether the medical community generally recognizes that NDMA causes cancer is unequivocally yes, your Honor. Every single regulatory -- next slide, please. I'm sorry, can you go back two slides.

Every single scientific or regulatory authority in the world agree that NDMA is a genotoxic carcinogen. The Defendants admit that NDMA is a genotoxic carcinogen. Your Honor, this has been established since 1978, when IARC first undertook an evaluation of this substance, and what they found was that NDMA is a probable human carcinogen, meaning it is a likely human carcinogen, and should be regarded for practical purposes as if it were carcinogenic to humans.

Now, IARC determines whether an agent is a carcinogen through a very rigorous process. They convene an expert panel of scientific experts in multiple disciplines from all around the country, all around the world, and all of those scientists gather all the relevant data information, look at the quality of the studies and read it, then they weigh the evidence and make a determination on the carcinogenicity of the agent. That

is what IARC did in 1978. It is vetted across a large group of experts and it is meant to simulate a peer review process by doing it in a panel format.

Defendants make much of the fact in their papers that the human evidence is limited and therefore IARC has not classified NDMA as a Category I known human carcinogen. That was true in 1987, which is the last time that IARC actually reviewed NDMA as a carcinogen. It was in 1987, your Honor. At that point in time the epidemiological evidence in humans was limited, but since then dozens and dozens of studies have come out in peer reviewed publications that establish an association between NDMA exposure and cancer, and that increased risk is evident whether the exposure is through diet, whether it is through air, whether it is through water, whether it is through Ranitidine, or whether it is through other drugs.

IARC has never re-evaluated the classification since that point in time in light of all this additional human epidemiological evidence that has come out.

Your Honor, Plaintiffs' experts are well suited to recognize this because multiple of Plaintiffs' experts have served on IARC working group panels. Dr. Melnick has reviewed over a hundred agents for carcinogenicity for IARC. Dr. Zeiger has sat on the expert IARC working group panels, Dr. McTiernan has sat on IARC expert working group panels. They are well suited to undertake this issue.

The Defendants have not proffered a single expert that has been an invited expert on an IARC working group panel to look at the carcinogenicity of an agent.

In 2002, your Honor, the World Health Organization issued a report -- I am not sure what is going on with my slides, bit it is not following what I am doing.

In 2002 the World Health Organization issued a report which said that NDMA is clearly carcinogenic, and highly likely to be carcinogenic to humans at relatively low levels of exposure.

This report -- I know your Honor is already familiar with it, but this report included a review of the dietary NDMA epidemiology at that time, in 2002.

What the World Health Organization determined was that the evidence in 2002 fulfilled in part the traditional criteria for causality, and that can be found on page 22 and 23 of the World Health Organization report, the 2002 report.

Since 2002, there have been dozens of peer reviewed studies in well respected journals that demonstrate an increased risk of cancer with exposure to NDMA.

Most recently, your Honor, in 2022, the Agency for Toxic Substance and Disease Registry, which is typically referred to as the ATSDR, they determined that there were human epidemiological studies demonstrating associations between exposure to NDMA and various cancers. In fact, ATSDR evaluated

the same dietary and occupational studies that Plaintiffs' experts evaluated, and they concluded that the carcinogenicity of NDMA is widely recognized, that can be found on page 4 and 5 of the 2022 ATSDR review of NDMA.

Last, your Honor, and most tellingly, the Defendants themselves admit that NDMA causes cancer.

GSK, in 2019, after the news broke that Ranitidine contains NDMA, conducted a health hazard assessment pertaining to NDMA, and they did it because the news broke that Ranitidine contained NDMA.

What they did was, and this is really telling, GSK evaluated the animal mechanistic and human epidemiology, including the dietary NDMA studies that Plaintiffs' experts evaluated, and they found that NDMA is a genotoxic carcinogen and exposure should be reduced to the extent possible.

GSK came to the same conclusion as the World Health Organization in 2002, and they concluded it is considered highly likely, highly likely that NDMA is carcinogenic to humans, potentially at low levels of exposure. This was on September 25, 2019, your Honor.

GSK further admitted that there is no qualitative differences in metabolism of NDMA between humans and rodents or other animals and that there is no reason to believe that humans would respond qualitatively differently.

GSK also, in 2019, examined the human dietary NDMA

studies and found evidence of a positive association with evidence of dose response for NDMA and gastric cancer, among others, and they also found that there was consistency among studies.

Defendants' company witnesses also admit that NDMA is a genotoxic carcinogen besides GSK. BI agrees that NDMA was a carcinogen. The head of Boehringer Ingelheim's pharmacovigilance, Dr. Robert Buchberger, admitted that NDMA is a carcinogen and it should be evaluated closely. Pfizer agreed than NDMA is a carcinogen, Dr. Arthur Ciociola, who is the VP of research and development. Sanofi agreed that NDMA was a carcinogen, Dr. Claude Kugel, Sanofi testing head.

And, your Honor -- my slides are not keeping up with my presentation, but if you look at our slide deck, and I know that you have a copy of it, there is a picture on slide 14 of animals exposed to Ranitidine that also showed signs of cancer, and they show the effect of Ranitidine on cancer metastasis, and what you see when you look at that picture, which should be the next slide -- the next slide, the next slide -- okay, it is lagging.

Your Honor, once you look at that picture, what you will see is there are mouse organs on the right-hand side that were exposed to NDMA in Ranitidine and they are laden and riddled with tumors. The mouse organs in the left-hand side were not exposed to the NDMA in Ranitidine, and you can see a

noticeable difference in those two pictures. A picture is really worth a thousand words.

Last, your Honor, Dr. Zeiger, who is one of the Plaintiffs' experts in this case, he is a member of the FDA working group on nitrosamines and pharmaceuticals and extensively published in this area, and Dr. Zeiger, he opines that the carcinogenicity of NDMA has been established, well established among the scientific and regulatory communities in the U.S. and internationally for more than 50 years. NDMA is generally accepted by the scientific and regulatory communities in the U.S. and internationally as a genotoxic and carcinogenic.

Tellingly, your Honor, Defendants have not moved to exclude the opinions of Dr. Zeiger. He is not subject to any of the motions that we are presenting this week. His opinions are unchallenged and they are unrebutted.

There is simply, your Honor, no genuine dispute of material fact that the NDMA, including the NDMA in Ranitidine, is a genotoxic carcinogen, and that is why Ranitidine has been recalled globally. The same holds true for every other drug that has been found to contain NDMA, whether that is Valsartan, Metformin, or Nizatidine, they have all been recalled because they contain a carcinogen.

Unlike zinc in Fixodent or Benzene in gasoline, which are some of the cases that Defense cite to, NDMA has no

beneficial practical purpose. It is exclusively used to induce cancerous tumors in laboratory experiments.

In fact, the pharmaceutical industry routinely uses NDMA as a positive control in carcinogenicity studies, and there are studies that have been produced in this very litigation, your Honor, where pharmaceutical companies have used NDMA in this fashion. Plaintiffs' experts also routinely use NDMA to induce cancer in animals, as do Defense experts such as Dr. Gingrich.

Your Honor, moving on to the second category under McClain for a toxic tort, that is conducting a general causation -- a full Daubert analysis on general causation, and it is to determine whether or not Plaintiffs' experts' methodology is reliable.

The question at -- in that scenario is whether Plaintiffs' experts applied reliable methodology such that their testimony could assist the jury in determining whether the NDMA in Ranitidine is capable of causing bladder, stomach, esophageal, liver, and pancreatic cancer.

Now, two Courts have already evaluated this issue and determined that the answer to this question is yes. First, Judge Kugler in the District Court of New Jersey, under a Daubert standard; and second, Judge Smith in the Illinois State Court under a Frye standard.

Plaintiffs are confident, your Honor, that when you

finish your review and evaluation of all of the methodologies and the evidence that the Court will also find in favor of Plaintiffs on this issue.

So, going to the traditional Daubert inquiry, there are three requirements. The first is qualifications, the second is whether the methodology used is reliable, and the third is whether the testimony assists the trier of fact.

Now, Defendants are not disputing that Plaintiffs' experts are not qualified in this case. So, the question is really going to come down to whether the experts applied reliable methodologies such that their testimony could assist the jury in determining whether the NDMA in Ranitidine is capable of causing cancer. Plaintiffs submit that the answer to this questions is yes, your Honor.

Daubert is about the methodology, not the conclusions, and our experts' methodologies are unassailable and have been highly recognized in the Eleventh Circuit and elsewhere as reliable and sound. All of our experts have analyzed the issue the same as they would in their professional practices. They have conducted a search of all of the relevant literature. They evaluated and weighed the evidence using their scientific judgment and expertise, and they found reliable association and applied the Bradford-Hill factors to determine whether there is a causal link.

Your Honor, if you look at a plain reading of our

experts' reports, they discuss how they reviewed the evidence with the same rigor that they use in their other work, and what Plaintiffs' experts have done, and that is all of them across the board, Dr. McTiernan, Dr. Moorman, Dr. Salmon, Dr. Le, Dr. Panigraphy, Dr. Michaels, they all looked at the totality of the evidence, they weighed that evidence using their own professional judgment, they found a reliable association and consistency across multiple categories of evidence, and then they applied the Bradford-Hill factors and they reached their causality opinions.

Bradford-Hill has been found to be a reliable method under Daubert in this Court by your Honor in the past, as well as in a multitude of Circuit Courts around the country, and it is also set forth in the Reference Manual for Scientific Evidence as a reliable methodology applied by experts.

Now, your Honor, scientists may reliably apply the Bradford-Hill factors but reach different conclusions, and as long as they are using their scientific judgment and expertise, they are explaining why they find certain studies informative and why they find other studies not informative, and they explain all this and reach their conclusion, then those experts should be permitted to proceed to a jury for a factual determination.

It is about the methodology, not the conclusions, because the same -- similar experts in a similar discipline can

look at the same evidence and they may weight it differently, and that is an issue for the jury to decide.

They can apply the Bradford-Hill factors reliably and reach different conclusions, and that is permissible under the law. Judge Rodgers in Abilify states that in her opinion.

Your Honor, you have aptly noticed in the past that the gatekeeping role is limited under a Daubert analysis. It is not intended to supplant the adversary system, the cross-examination, or the role of the jury, and the real role of Daubert is to keep true junk science out of the courtroom. It's to keep junk science away from a jury, and that is not what we have here.

There is a huge body of evidence that supports our experts' opinions and all have been cited to extensively in the reports. There have been more than 500, 600 references that these experts rely upon to support their opinions.

Going back to Eleventh Circuit standards, in Abilify Judge Rodgers listed the three primary methodologies that experts can rely upon un reaching their opinions. One is epidemiological studies; two is assessing a dose response relationship; and three is a background risk of the disease.

It is not required that the experts meet all of those methodologies, they only need one, your Honor, and that is noted by Judge Rodgers in the Abilify opinion. What we have here is the experts cite multiple supportive studies for each

cancer that demonstrate an association between exposure to NDMA, including the NDMA in Ranitidine, and the five cancers at issue here. So, there is consistency across all categories of evidence.

In addition, experts who have reliably applied the three primary methodologies can also bolster their opinions with secondary methodologies. Those secondary methodologies, which should be on the next slide if my PowerPoint is keeping up with me -- here we are.

The secondary methodologies are biological plausibility, case studies, adverse event reports, animal studies, and in vitro studies. What we have here, your Honor, is the Plaintiffs' experts relied on all of these methodologies. They looked at all of the primary methodologies, as well as all of the secondary methodologies. They considered all of it, and what they found were consistent trends across all categories of evidence, and that is how they reached their conclusions.

Next slide.

So, your Honor, one of the things that we have heard about today quite a bit is dose response. I think it is important to really discuss what dose response actually means.

Dose response is evidence that a change in the amount of exposure is associated with an increased risk, and simply put, if the amount of NDMA exposure increases, the risk of

cancer increases.

In this case there is evidence of dose response, it is in animal studies as well as in human epidemiological studies, but this shouldn't be conflated with dose. Dose response as a scientific concept is different than dose, which is an individual case specific causation inquiry as whether or not a Plaintiff had enough dose of the toxin to cause their injury.

Dose response is evidence in the scientific studies that the increase in exposure caused an increase in risk. It is as simple as that, your Honor, and there is that evidence across multiple studies, which Mr. Nigh will discuss shortly, as long as I haven't used up all of his time.

Your Honor, Mr. Petrosinelli pointed out very clearly that in McClain versus Metabolife that the experts need not quantify the precise numbers about a dose response relationship. It is enough to show that dose response exists in the epidemiological studies.

Your Honor, I want to address some of the other arguments that Defendants have made that are without merit.

The appropriate question is whether the NDMA in Ranitidine can cause cancer at the highest realistic dose any one Plaintiff in this litigation may have been exposed to. It is not the minimum dose, it is the highest dose.

Secondly, there has been found to be a reliable association such that a Bradford-Hill analysis was appropriate.

In fact, their own internal toxicology experts who reviewed this issue founded an association. So, to sit here and say there is no association is just not credible.

Your Honor, additionally, the NDMA and the Ranitidine epidemiology are both relevant to the question of whether the NDMA in Ranitidine causes cancer. Both categories of evidence are relevant to this question. We cannot lose sight of the fact that this case is about NDMA, which is the carcinogen in Ranitidine.

This case is not like the Benzene cases and it's not like the Chapman and Fixodent cases, and I will explain why in a moment.

Going back to the first issue, which is about the highest possible dose, for purposes of general causation we respectfully direct the Court's attention to the Roundup Daubert opinion as persuasive authority where the Court acknowledged that at the general causation phase Plaintiffs need not establish any particular level of exposure, but that Plaintiffs only need show that the agent can cause the disease when people are exposed to the highest dose that people might plausibly experience.

To put that into context, your Honor, in this case, in the registry more than 60 percent of the registry claimants had exposure for more than ten years. Okay. And that is a really important point when we are evaluating some of the Ranitidine

epidemiological studies that Defendants cite to as being so informative. They are not looking at Plaintiffs that have chronic use like we have in this case.

Your Honor, Defendants have tried these identical arguments about there not being a reliable association, such that a Bradford-Hill analysis was inappropriate, that Mr. Petrosinelli just said to you previously. They tried these arguments in Valsartan and Judge Kugler swiftly shut them down and, your Honor, he also determined that Bradford-Hill and weight of the evidence are acceptable methodologies to assess this issue and permitted all of the Plaintiffs' experts to proceed forward. He actually excluded several of the Defense experts for not reliably assessing the issue.

Your Honor, Courts often look at the underlying chemical in a product in a toxic tort such as this. In certain cases, for example, the Benzene cases that they cite, it is about Plaintiffs who are exposed to Benzene in gasoline, and the Burst case, which is one of the cases that Defendants cite to, actually supports our experts being permitted to proceed because in Burst they excluded the expert because the expert only looked at the Benzene studies and did not look at the gasoline studies.

The expert in Burst actually went so far as to say the gasoline studies are irrelevant, are irrelevant to the issue, and that, the Court found, was not reliable methodology, to

completely ignore one category of evidence that is relevant to the causation inquiry.

Here, your Honor, Plaintiffs' experts looked at both the Ranitidine epidemiology and the NDMA epidemiology, so it differs from the Burst case. The experts here looked at all of the relevant evidence to reach their conclusions and they found consistency throughout.

In addition, your Honor, there is the Henricksen case, which Defendants also cite to, which is an opinion also about an exposure to Benzene in gasoline, and that particular case same thing, it said, because gasoline exposure is a source of Benzene exposure, which Benzene was the carcinogen at issue in that case, evaluations of both the gasoline and its toxic component Benzene are obviously relevant to the Plaintiffs' case, and that is what we have here, your Honor.

Going and looking at the Chapman and the Fixodent cases, which are also cases that Defendants cite to in their papers and have cited to up here, again, it is not like this one.

In those cases, there was no, zero, supportive epidemiology regarding the substance or the toxin at issue, there was none. The toxins that were being addressed were not identical.

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. The compounds were different and there was evidence that there were differences in the bioavailability of the zinc calcium compound compared to the zinc acetate compound.

There is no such evidence here that NDMA in Ranitidine is any different from NDMA in the diet, or NDMA in contaminated water, or NDMA from inhalational exposure at work. There is no evidence that has been proffered by Defendants to suggest there is a difference.

Your Honor, there are forest plots in my presentation, which, as I said, is lagging so it is not up on the screen, but -- there it is. You can see here, this is the Ranitidine epidemiology on these forest plots. This is only Ranitidine epidemiology, and for all of the five cancers you can see that there are multiple studies, not all, but there are multiple studies that show a point estimate to the right of 1, which demonstrates an increased risk.

Mr. Nigh will go through that in more detail shortly.

So, your Honor, just to sum it up briefly, given the fact that each expert in this case that the Plaintiffs have offered have conducted a comprehensive search of the literature the same way that they would do in their own practice, they reviewed all of the relevant evidence, they evaluated the strengths and the weaknesses of the studies, they articulated that in their report, why they found certain studies to be

informative, why they found studies that were not informative, and they found an association, and once they found that association, based on the totality of the evidence, they applied the Bradford-Hill factors in reaching their conclusions, which is a reliable methodology, and their opinions should be permitted to proceed to a jury for a factual determination.

Last, your Honor, there are a couple of things that I want to address that were in the slides that we were provided by Defendants yesterday. I feel like I need to address some of the misstatements in some of those slides.

First, on slide 30 of their presentation they put up a chart, you might recall, and it had a whole bunch of different organizations on it, American Cancer Society, American Lung Society, Pancreatic Cancer Network, all the different organizations, and they state that no medical or scientific organization identifies an association between Ranitidine use and any type of cancer, and they list all of the organizations, plus a dozen more that I just mentioned.

Your Honor, there is not one shred of evidence that a single one of those organizations that they put up on the screen has ever assessed the question of whether Ranitidine use is associated with any type of cancer, zero evidence.

You know what those organizations do recognize? That NDMA can cause cancer. That is what they do recognize.

Secondly, Defendants state on slide 9 of their presentation that independent researchers studied the Ranitidine question, and then they provided a dozen or so slides to support that these researchers found that Ranitidine does not cause cancer.

This is a blatant misrepresentation of the evidence. An independent researcher who conducts a single study cannot state with certainty that Ranitidine does not cause cancer. That is not how the epidemiological studies work.

The same holds true for the Florian study, none of these researchers have evaluated the totality of the evidence beyond the four corners of their own study, so they cannot make that determination.

No one has conducted a systematic review of all of the evidence to assess causality except for Plaintiffs' experts. It did not happen and to suggest that an individual researcher who conducted a single study could conclude that Ranitidine definitively does not cause cancer is just false.

The most that they could represent is that an individual researcher did not find evidence of an association in the four corners of their study, and Mr. Nigh, my colleague, will explain to you why the findings aren't a surprise based upon the study design.

Just to put it in perspective, your Honor, for example, a study that is designed to assess the carcinogenic

effects of smoking one carton of cigarettes likely won't find an increased risk of cancer, but we know that smoking causes cancer. That has been established. The best that that study can tell you is that smoking one carton of cigarettes doesn't demonstrate an increased risk of cancer in that particular study. You have to look at the strengths and the weaknesses of each individual study to reach a conclusion.

Third, the independent researchers that Defendants put up are not so independent. The Adami study was conducted by consultants for Sanofi in this very litigation, have not been disclosed by Defendants. They were not independent. To suggest they were is simply not true.

Last, your Honor, one point that I would like to bring to your Honor's attention. You have instructed us not to -- arguments that have not been briefed at the hearing today. Based upon our review of the presentations that were provided to us yesterday, it seems apparent that there will be new arguments being made at the hearing for certain experts that were not addressed in the briefing, and to the extent that your Honor considers those, we may be requesting an opportunity to file a surreply to address those arguments because they were never raised in the original briefing on this case.

My colleagues will identify when that is the case during their arguments about the specific experts.

With that, your Honor, I am going to turn over the

floor to Mr. Nigh, assuming I haven't used all of the time, and I will let him talk to you about epidemiology and dose.

Thank you.

*THE COURT:* Okay. Thank you very much. You have used 35 minutes.

*MR. NIGH:* Could we go to slide 59.

Good morning, your Honor, Daniel Nigh for the Plaintiffs, may it please the Court.

*THE COURT:* Good morning.

*MR. NIGH:* Your Honor asked about, in your questions that you presented to us, the dose response of NDMA and Ranitidine, including how much NDMA and for what length of time a person must ingest NDMA and Ranitidine to cause the designated cancers.

Now, the Defendants, in their presentation, would seem to pretend that we never addressed this question, and I am floored because it is actually extensively addressed in Dr. Salmon's presentation. There are numerous pages on this. The same thing for Dr. Panigraphy, it is extensively addressed. Dr. Salmon does an extensive analysis to show the lifetime cumulative exposures of NDMA it would take to statistically -- to reach a statistically significant increased risk of the five cancers in the NDMA studies. Dr. Panigraphy does this as well.

Now, again, Mr. Cheffo stated that it is stunning that Plaintiffs have offered no experts on the dose that would lead

to increased risk of cancers. Of course we did. That is in there. Dr. Salmon also demonstrates how long Plaintiffs would need to ingest Zantac to reach the lifetime cumulative exposures of NDMA it would take to reach statistically significant increased risk of the five cancers in the NDMA studies.

This slide is an excerpt of the chart that shows precisely that. Dr. Panigraphy does this as well.

Lifetime cumulative exposures addressed by Salmon and Panigraphy address how long, how often, and how much Ranitidine use it would take to reach the increased risk of cancers demonstrated in the NDMA dietary and occupational exposure studies.

Dr. Salmon ties this analysis to whether we only look at Defendants' and FDA's baseline testing. So, if you only consider that, that is the first column under baseline. That shows how many years it would take to reach lifetime cumulative exposures that would have led to increased risk for each of these cancers. That column is there.

The very next column shows the other part of the equation is that the baseline testing levels, as we'll demonstrate as we get further to Dr. Najafi's presentation on day two, are only a small part of the equation. That is what is the NDMA before the consumer ever even purchases the product and opens up the bottle and places it in a common

place. Even so, the baseline is even under represented because it doesn't demonstrate how long these products may be in the shipping and supply chain.

Many of the products are a much longer period of time. We have demonstrated evidence in this case that some products actually take years from the time they are manufactured as a finished dose product until the time that the consumer even purchased the product, let alone that the consumer has the expectation with a three-year expiration date that they can use that product through to the end of that three-year expiration.

Dr. Salmon also ties the analysis to that second part of the equation, what happens after you open up the bottle, what happens as a result of these other conditions, and when you add in or look at the extra amount of NDMA that is actually forming inside of the product, how long does it take to get these five cancers based on the NDMA dietary and occupational exposure studies.

How long does it take to get these cancers, that is the complete story, and that is the column on the right. We can see under that analysis, that analysis is how long does it take to get statistically significant increased risk seen in the dietary and the occupational exposure studies.

Finally, for bladder cancer, based on Ranitidine epidemiology alone, Dr. Salmon also calculated cumulative exposures to reach statistically significant increased risk of

bladder cancer from Ranitidine use, and demonstrated that Plaintiffs will obviously reach those cumulative exposures in this litigation.

He couldn't calculate cumulative exposures for the other four cancers based on Ranitidine epidemiological studies alone because none of the other Ranitidine studies had the defined daily dose, known as DDD, information necessary to do a cumulative exposure calculation.

In all of the Defendants' briefing they never adequately or specifically attack Dr. Salmon's or Panigraphy's lifetime cumulative exposure calculations. It is being raised for the first time today.

In the Valsartan MDL, another NDMA contaminated medication case, this was extensively addressed, and there are numerous cases that admitted evidence of lifetime cumulative exposures, similar to the lifetime cumulative exposure analysis that Dr. Salmon did, and they are admitted for the purpose of both proof of the dose question both for general causation and specific causation, and this is precisely why these lifetime cumulative exposure calculations were admitted in the Valsartan MDL as proof of the dose question for general causation and should be admitted in this Court.

I would also like to point out that one of the slides that the Defendants raised on the Chhabria decision tried to suggest that our standard is higher here than the Ninth

Circuit, but that slide also says, as the Third Circuit and the Eleventh Circuit, the Valsartan MDL is in the Third Circuit, and this opinion has been admitted in the Third Circuit.

In addition to that, Salmon also demonstrated through thorough analyses regarding dose response relationship for each of the studies.

Let's turn to page 52, slide 52, please.

Now, next I want to address the Defendants' markup of our bladder cancer forest plots.

As I understand the Defendants' methodology and their approach to this case, for the Defendants to prevail in showing no association between Ranitidine use and bladder cancer the Defendants must hit the royal flush, or the superfecta, or the triple bars on the slot machine. They have to line up on every one of these arguments and take away every one of these to demonstrate no association.

Let's talk about why it is not true. The dietary studies.

First, they must convince your Honor that no reliable expert would ever include NDMA dietary studies in their analysis whatsoever. Well, even GSK and the EMA included NDMA dietary studies in their analysis.

Second, Hidajat, they must convince your Honor that no reliable expert would ever include Hidajat in their analysis whatsoever. Again, even GSK and the EMA, when they were

looking at the issue of Ranitidine and cancer, included those studies in their analysis.

Third, they must convince your Honor that because one Plaintiff expert gave Habel no weight, that no other Plaintiff expert can give Habel any weight whatsoever, which simply is not the legal standard, and the Defendants have not established that that is the legal standard.

Fourth, they must convince your Honor that no reliable expert would ever include crude risk estimates in their analyses, even when the adjustments in the study are not well documented and questionable, which again simply isn't the legal standard and the Defendants have not established this.

Fifth, next the Defendants cherry pick their best result in a sub analysis. We don't have any sub analyses on this chart. We don't have what happens after one year lag, five year lag, ten year lag, unless they didn't give us a primary analysis without that in the study. That is what each of the forest plots do, they just give you the primary analysis in the study and every study that looked at the issue of Ranitidine and cancer, and/or NDMA and cancer.

So, the Defendants cherry pick their best results included in the forest plot. Even though that finding is not statistically significant they inject it in there.

But there are numerous sub analyses even in the Norgaard study that they avoided including, including that when

a ten-year lag is applied for bladder cancer there is a statistically significant increased risk of bladder cancer for Ranitidine users compared to H2RA users, and the same is true for Ranitidine users compared to PPI users when applying only a five year lag period.

They omit the longer lag time analyses for Norgaard despite insisting upon inserting the longer lag time in the Liu for the gastric cancer.

Also, for Cardwell, they didn't insert the statistically increased risk for long-term exposure for Ranitidine users compared to nonusers, for Ranitidine compared to PPI, and the non-statistically significant increased risk for long-term exposure for Ranitidine compared to H2RA. Any way you look at that study, the long-term risk in Cardwell are elevated for Ranitidine compared to whichever group you look at.

Now, there are numerous more favorable sub analyses that show increased risk, with many being statistically significant. In this case we have -- between these various studies there are thousands of sub analyses, and the Defendants are cherry picking a few to put on their forest plots.

We did not include these sub analyses on the forest plots; however we will later show that even with the forest plots created by the Defendants' experts with the sub analyses that the Defendants' experts chose to include, that there is

clearly an association between Ranitidine use and bladder cancer.

Finally, they must convince your Honor that significant results could not be included that statistically -- non-statistically significant results cannot be included by any reliable expert methodology. Even though the reference manual does not require rejecting non-statistically significant results, the Supreme Court of the United States discusses how experts are permitted to include non-statistically significant results, and the American Statistical Association encourages considering results regardless of whether the P value crosses .05. That is an update in 2016.

Now, in the interest of time, I won't go through the Defendants' manipulation of the rest of out forest plots for the other four cancers as my same arguments made for their manipulation of the forest plots for the bladder cancer would also apply to the other four.

Can we go to slide 60.

Now I will talk about statistical significance.

The reference manual specifically states that epidemiologists have become increasingly sophisticated in addressing the issue of random error and examining the data from a study to ascertain what information they believe about the relationship between an agent and a disease, without the necessity of rejecting all studies that are not statistically

significant.

So, the reference manual doesn't follow rejecting the non-statistically significant studies, as the Defendants have done in the forest plots.

Next slide, please.

The FDA relies on data that it is not statistically significant. The Supreme Court of the United States, in 2011, points this out. The FDA similarly does not limit the evidence it considers for purposes of assessing causation to statistically significant results.

Next slide.

Statistical significance is not required by the law. They also state, the Supreme Court, Courts frequently permit expert testimony on causation based on evidence other than statistical significance. As these Courts have recognized, medical professionals and researchers do not limit the data they consider to the results of randomized clinical trials or to statistically significant evidence.

Next slide. Actually, if we can go now to the first slide.

Now, I also want to address one more thing the Defendants raised. The Defendants assert in broad strokes that the same data analyzed by Dr. McTiernan and Moorman for rejecting the five cancers that were not designated is the same data, or comparable data, for the other five designated

cancers, but this is utterly false.

It is easy to explain with kidney and breast cancer briefly. Neither kidney nor breast cancer demonstrates increased risk of cancer due to exposure to NDMA in the Hidajat occupational study. On the other hand, the five designated cancers do demonstrate this.

In addition, kidney nor breast cancer demonstrate increased risk of cancer in the dietary studies. That specifically assessed exposure to NDMA. On the other hand, most of the five designated cancers do.

What I want to do now is, I want to discuss the topics that I am going to go through in my presentation.

I want to show first off that the Ranitidine epidemiology itself shows increased risk for the five cancers. We are going to discuss the Y.D. Kim study because it is the study on the forest plots that the Defendants present in their papers, and it is an outlier. It is one of the only studies that shows a statistically significant decreased risk.

Other Ranitidine active comparator studies that I will talk about, how they would bias results toward the norm, but even with that bias, many of those studies show increased risk and statistically significant increased risk, and then also, the NDMA dietary and occupational studies, and then we will talk about the dose response and is there enough dose for general causation, which I covered somewhat already.

Let's go to the next slide.

First, the Ranitidine epidemiology shows increased risk for all five of the cancers that we are looking at here today, and not just increased risk, but statistically significant increased risk, and then there are other studies that also show increased risk in addition to that.

If we can go to the next slide.

First, the Cardwell study for bladder cancer shows that overall a 22 percent increased risk when you compare Ranitidine users to nonusers, also when you compare Ranitidine users to PPI users, statistically significant increased risk. When you are looking at three plus years, 43 percent increased risk, statistically significant when you compare Ranitidine users to nonusers. Also statistically significant when you compare Ranitidine users to PPI users, and non-statistically significant increased risk when you compare Ranitidine users to H2RA users.

Next, next slide.

But in addition to that, we can see multiple other studies. Every study on bladder cancer, the primary result is to the right of 1. Every study demonstrates an increased risk of bladder cancer. The Habel study, 56 percent increased risk. That one combined kidney cancer and bladder cancer. Had they just looked at bladder cancer it may have been even more of an increased risk.

Norgaard, 11 percent increased risk. Kantor, 30 percent increased risk. Yoon, 41 percent increased risk.

Next slide, please.

Gastric cancer, Liu, when they apply a one year lag. They don't have a result without a one year lag, so we took that first result, 42 percent, statistically significant increased risk. Habel, the gastric cancer is combined with the esophageal cancer, but a 142 percent increased risk for those two combined.

Next esophageal cancer, Adami, 30 percent, statistically significant increased risk. Habel, 142 percent increased risk. Adami, 9 percent increased risk, not statistically significant.

Next slide.

Liver cancer, 91 percent, statistically significant increased risk when you compare Ranitidine users to nonusers.

Next.

Kantor compared to Lansoprazole, still a 15 percent increased risk. Now, it is important to understand, as the authors have also discussed in many of these studies, that PPI also has multiple studies that carry -- that demonstrate an increased risk of liver cancer, but Kantor, 15 percent increased risk, not statistically significant. Tran, 41 percent increased risk when they used the Scotland database. When they used the U.K. bio bank, 82 percent increased risk.

Next.

For pancreatic cancer, McDowell, 37 percent, statistically significant increased risk, and Habel, 160 percent increased risk.

Those are the epidemiological -- the Ranitidine epidemiology, and we would submit to your Honor that the Ranitidine epidemiology is actually quite favorable for these five cancers.

In addition, we want to address some of the shortcomings of the Ranitidine epidemiology, and a lot of the reasons as to why the Ranitidine epidemiology cannot be taken alone, but you must look at the other epidemiology in terms of the NDMA in the diet and the NDMA in the occupation, because that is the carcinogen.

Next slide.

Now, the Defendants would raise that there are some statistically significant increased risks on one side, there are some statistically significant decreased risks on the other side, so they kind of wash out. Really what wasn't raised and what you don't see in those forest plots is that nearly every one of the statistically significant decreased risks is one study alone, the Y.D. Kim study. We will talk about that.

Next slide. Next slide, please.

Reality is that Kim is an outlier.

Next slide.

To understand some of the reason behind why Kim is an outlier we need to go back to when Kim was first shown to the world, and that is when it was shown to the world in the DDW 2020. This is where it came out. Surprisingly, Mohy-ud-din also came out around the same time. Mohy-ud-din never got published, but I am going to talk about a lot of the similarities between the two.

They both use the Explorer's database, that's the database of U.S. prescription users, and they both have a similar timeframe. Then, in addition, they both compare Ranitidine to Famotidine, and then they are also both abstracts of the DDW 2019.

Next slide.

Now, we got internal documents from the Mohy-ud-din study, and what those documents showed was that Mohy-ud-din actually went a step further. Using the same Explorer's database they compared Ranitidine users to nonusers, but Kim never looked at that issue, and that is why this is extremely important, because when you compare the incidents of cancer with Ranitidine versus general population, with adjustment for risk factors, you get results that are wild and it explains something wrong with this database, just terribly wrong.

We are not standing up here today to say that studies should demonstrate what this study did, a six fold increase in all cancers, 600 percent increase of all cancers. Looking at

ours, pancreatic cancer, an 878 percent increased risk; bladder cancer, a 989 percent increased risk; liver cancer, 912 percent increased risk; esophageal cancer, 1,039 percent increased risk. Those are wild results and they demonstrate a serious flaw with the Explorer's database altogether.

Let's take a look at the next slide.

We are going to discuss what some of those flaws likely are in the Kim database, some of the signals that gave us. The Kim Y. D. database even admits that the Ranitidine cohort consistently displayed lower prevalence of common risk factors for gastrointestinal malignancies. It may be that when adjusted for every common risk factor for each cancer the adjusted ORs for the Ranitidine cohorts may increase.

Next slide.

What does this mean? Well, when we compare ranitidine to Famotidine, we see some issues that show that the Y. D. Kim study does not meet that Federal guidance -- guideline that the Defendants showed earlier to compare a similar population of users. The Famotidine users are not similar to the Ranitidine users.

Tobacco use, the Ranitidine (sic) users smoked more, they drank more, they had diabetes more often, they were obese more often, they had cirrhosis more often, they had IBD, irritable bowl disease, more often, they had gastritis more often. These are all risk factors for cancer.

Next slide.

The Mohy-ud-din study even looked at some risk factors that Kim never looked at and found even more problems that obviously wouldn't have been adjusted by Kim.

We asked Dr. Wang, the Defense expert, Doctor, as you considered the Kim study, did you consider the Famotidine population is a more diseased population than the Ranitidine population? Well, I guess this is a recent set of data and in these studies it is a little unclear. You just presented both abstracts and it does appear that they both appear to show that the risk factors we discussed were lower in the Ranitidine cohort.

Next slide.

Often times a picture is worth a thousand words and the picture demonstrates this.

Incident rate charts often times are fantastic to be able to determine if you are looking at the more diseased population, otherwise discussed as protopathic bias in some regards, or -- and then over time you can look to see is the amount of cancers increasing or decreasing between those two comparators.

What you will see is even in the Kim Y. D. study the Famotidine users were a more diseased population right out of the gate. They have a much higher increased incident of cancers, and that is all the way through until you get down and

you start to see the gap narrow, years seven to eight, eight to nine, and nine to ten.

This is the reason why long term followup is extremely important, especially when you start from behind, because if we had actually gotten further along we may have been able to see in this study do the results now flip and Ranitidine long term is more cancers than Famotidine. The key here is, if it is short term, a lot of times the short term is not going to be due to a carcinogen from ingesting the drug. Most of those take a longer period of time.

Now, we are not saying it can't happen short term, but the majority of them, and the vast majority of them, happen long term. So, what is happening short term? Those are the risk factors that the individual people exposed in the group, that is what they are bringing to the table. That is the short term on an incident rate.

Now let's look at the next chart. Recent epidemiology that has not yet been peer reviewed and published, I will represent that, but in terms of getting these sorts of incidence rate charts that are very valuable, it shows exactly what we are saying, that pancreatic cancer, when they compared non-Ranitidine users to Ranitidine users, you will notice at the very beginning they are pretty tight, pretty close. That is not strong evidence of protopathic bias.

What you see over time is the gap widens, over time

the risk from Zantac becomes more and more apparent.

Next slide.

In liver cancer we see the same thing, tight at the beginning and over time we see the separation between the two.

This is why time and time again we are encouraging that these Ranitidine active comparator studies, the biggest flaw they have is just short-term followup, and you need long-term followup to be able to see a lot of these risks, to see the separation.

Next slide.

Gastric cancer, we see the same thing, tight at first, separation thereafter.

Next slide.

Even in the Norgaard study, we got a draft of that publication and I will represent to your Honor that the Norgaard study, to call this an independent study is a stretch. It has all the same authors as the Adami study except they took off the Sanofi author and they took off the exponent author from Adami, and it is set up very similar.

If you look at the study itself, the charts even all look similar because they obviously followed the template of what had occurred with Adami and the other, the exponent author, beforehand.

Now, what this draft showed is that the increased risk of bladder cancer for Ranitidine users over time separates.

This incident rate chart never made its way into a published study, we'd represent quite likely because of the bias.

Next.

Now, Defendants cherry picked the FDA guidance on active comparators. It actually says selection of an appropriate comparator group or control group, but a control group means user versus nonuser. They are not saying that it is ideal, it is better to do an active comparator versus a user versus nonuser. They are saying you can look at each of those, but if you are going to do -- in cohort studies, if you are going to do a comparator study, it is ideal to use a group taking a drug used to treat the same disease with the same level of disease severity.

So we have demonstrated already why Kim does not live up to that ideal comparator. Famotidine is not the same level of disease severity as Ranitidine.

Next slide.

Now, I want to address a lot of shortcomings in these studies, but I will address them kind of as a whole in the interest of time.

They all have -- many of them have numerous flaws, most importantly is they don't have enough usage. The only one that demonstrates real long term usage and explains the amount of long term usage is the Cardwell study, and that one actually shows 1,095 DDD, that is the defined daily dose. They are

actually looking at is it 300 milligram, 150, 75. Well, DDD would be 300 milligrams, so they are actually looking at the dose and the amount of time for that dose and how often.

None of the other studies do that. The only ones that come close would be Adami and Norgaard, and they only have ten prescriptions. We don't know what those ten prescriptions are, that information is not in there. It could be one month, three months, we don't know, but if it is one month, that is only ten months of usage. That is not really long term usage.

Next, there is not a long enough followup -- actually let's go back to the slide before.

There is not a long enough followup, and this is crystal clear in the studies. All the study authors say the same thing, that they are not looking at long -- you know, looking at the full picture of cancer development, they are only looking at the front end of the bell-shaped curve.

They are missing important data on confounders. Adami and Norgaard are terrible for this, and we will talk about that later on. They are missing accurate exposure measurement, they are not accounting for over-the-counter use, Adami and Norgaard don't do this.

You will see when you look at what -- the experts have also analyzed this, and they recognized that the over-the-counter usage for Ranitidine users is much, much higher so they are not captured in Adami or Norgaard compared

to the other H2RAs, and compared to PPI. That is an extreme problem.

Some of these studies lump in Nizatidine with Ranitidine. We are not bringing a Nizatidine case here. We don't have any evidence on the amount of exposure -- on the amount of NDMA in Nizatidine. It is low. There is a reason Plaintiffs haven't brought cases on Nizatidine.

Next.

What do all these things do? Short term usage, short term followup, non-differential misclassification in the form of the problems with over-the-counter usage, or not capturing all the usage, a lot of these studies start decades after Ranitidine users would be using Ranitidine, and so if they switch to a PPI, no credit for the Ranitidine users, they push the results toward the normal. I will suggest even with that push and pressure towards the norm we still have plenty of studies, we talked about that at the beginning, that demonstrate increased risk for these five cancers.

*THE COURT:* You have about four minutes, that is giving you the extra two.

*MR. NIGH:* Okay. Finally, even the IARC says that experience from studies of cancers in humans indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years, therefore latency periods shorter than 30 years cannot provide evidence of lack

of carcinogenicity, but that is precisely what the Defendants are trying to use it for.

They are the ones trying to use it for lack of carcinogenicity, we are not, and the IARC says that is inappropriate.

Next slide.

This is how the epidemiology should be structured, you should have the -- on the top it should be 30 plus years, and you should separate the groups to where only the Ranitidine users are at the bottom.

Next slide.

This is what it actually looks like. You actually have some Zantac users that are in the top group because they would never know if they used Zantac, and then on the bottom, you don't have much exposure to the Zantac, and most of the studies are less than ten years. A few are just a little bit longer than ten years.

Next slide.

None of the Defendants' studies had a long enough followup. Kantor, Kim, Iwagami, Kumar, Tran, Yoon, they are all seven or less years, and each of these study authors admit this.

Next slide.

So you can see, they are all saying that it is not long enough. Yoon says the overall followup period is not long

enough to assess the onset of cancer. Adami says the most severe shortcoming of our study is limited number of participants with long term followup. Kantor says we did not capture long term outcomes. Iwagami, longer followup, especially among those with high cumulative dose may be warranted. Kumar, longer followup is necessary. They all address the same issue.

Even the reference manual discusses this, the absence of epidemiological data is due in part to the difficulties in conducting cancer epidemiology studies, including the lack of suitably large groups of individuals exposed for a sufficient period of time, long latency periods between exposure and manifestation of disease, the high variability in the background incidents of many cancers in the general population, and the inability to measure actual exposure levels.

I want to turn our attention to slide 57, and I will do this quickly.

We do have multiple studies that demonstrate a statistically significant increased dose response. We see it in the Cardwell study, Adami, Hidajat, Low, De Stefani, De Stefani 2001, Larsson, Lavecchia, Pobel, Ronca. These all demonstrate that as you increase the amount of Ranitidine, the amount of cancers increase, or if you increase the amount of exposure to NDMA, the cancers increase.

*THE COURT:* That would be your time. Are you done or

do you have another minute or two?

*MR. NIGH:* I have one more slide. It is slide 51.

Them Hidajat, we have heard Defendants argue that inhalation exposure is irrelevant for oral exposure issues. That is inaccurate. There is a formula for this that toxicologists commonly use, how to extrapolate from inhalation to oral. Why would they create a formula if you are not supposed to use it? It is used all the time.

They look at how do you compare skin absorption to oral, how do you compare inhalation to skin exposure. There are formulas for this because oftentimes we want to know the data in one study, we want to see what it would be like for another route.

Now, the FDA says to use caution when you are looking at this, but that is precisely what Dr. Salmon and Dr. Le did, they used caution and due diligence to see that the bioavailability from inhalation would be similar to the bioavailability from oral exposure. Dr. Le calculated it, greater than 90 percent gets into the bloodstream from ingestion. That makes it similar to the bioavailability.

With that, the other issue is that they would argue there is other carcinogens, rubber dust, rubber fumes. Dr. Hidajat in long detail explained that study measures the amount of exposure to NDMA in certain parts of the factory and the amount of exposure to rubber dust and rubber fumes in other

parts of the factory.

It actually shows in the vulcanizing department you get high amounts of NDMA, but not -- you actually have low amounts of rubber dust and rubber fumes. That exposure there lets us have confidence that the increased risk seen for NDMA is due to NDMA, not some unforeseen circumstance or some other carcinogen.

That is all. Thank you.

*THE COURT:* Thank you.

Okay, the Defense has an opportunity to present a rebuttal, and you had five minutes, but Plaintiffs went over by an additional two above and beyond the additional two they got, so you have seven minutes.

*MR. PETROSINELLI:* Mr. Cheffo gave me some minutes back, so I will talk a little bit, because he stole my minutes.

I am just going to do a couple of law points, Roundup, because I didn't get to address it. The framing of the general causation issue, I think I said before we agree because it incorporates the concept of dose.

There is one thing that Roundup says that the Plaintiffs showed, the opinion says, all the Plaintiffs have to do is show the highest dose that humans could be exposed to, and if they do that reliably, then they get all the other doses, too. That is not the law in the Eleventh Circuit. Chapman and McClain are clear that it is not about highest

dose, it is about lowest dose. You have to have a threshold dose and then dose response, so that is just not Eleventh Circuit law.

The second thing is the Roundup opinion makes reference to a reasonable jury standard, like what does a reasonable jury -- could a reasonable jury conclude about the evidence. That, too, is not the standard in the Eleventh Circuit, and honestly, I don't think is correct under Rule 702. It is a preliminary question for the Court. In other words, the Court has to make a preliminary, as the Eleventh Circuit says, threshold assessment of reliability.

I think your Honor knows this from your work with the Rules Committee, there is an amendment to Rule 702 that is about to happen, and the amendment is to address this very question, that there is some confusion about whether there is some reasonable jury standard or it is a standard for the Court, and the amendment is going to add the words "the proponent demonstrates to the Court" that it is more likely than not A, B, C, and D in the rule.

This is a hot topic in Rules Committee land, and it is clear that it has nothing to do with the reasonable jury standard, it is the Court that has to make the assessment.

The final thing, just a comment on what said about my piece, please, I urge the Court to look at Dr. Salmon's chart, as I know you will, that Mr. Nigh showed as their proof of that

response. Mr. Holian is going to address why the methodology that resulted in it is totally unreliable, but let's assume it was perfect methodology.

Look at some of the lines on the chart, kidney cancer, at a 900 nanogram dose, that was the highest FDA dose, he calculated it would take 47 years of use to have an increased risk of cancer. Done, stipulated, you can enter summary judgment right now on any kidney cancer case. No one took Zantac for 47 years.

That chart sort of highlights the need for the dose opinion, put aside whether it is even methodologically sound.

What you also heard from Mr. Nigh is the Zantac studies, the epi studies are too short, there is not enough information on dose, not enough followup. That is precisely why -- we don't agree with that, but that is precisely why in the Eleventh Circuit you must give the threshold dose and the dose response curve, and they don't have any evidence at all on threshold dose and any reliable evidence on dose response.

I will turn it over to Mr. Cheffo.

*THE COURT:* Okay. Thank you.

*MR. CHEFFO:* Your Honor, I think now we are even.

I just have three quick points. The first is, you saw a lot of those charts about increased risk, but what you didn't see, right, are what the study authors say they mean. You have what Mr. Nigh and his colleagues think they mean, but we didn't

hear or see what the study authors actually deal with.

We also heard that no study author can kind of make that determination because they are essentially inside. Well, that is certainly not true because they read the literature, but even if it was, that is what the EMA and FDA are for. They actually did look at all the data and they have determined essentially consistently that there is no association.

Counsel made a point of things outside the record, so I don't want to harp too much on this, but you saw things like draft studies or we got this Norgaard from some subpoena or wherever they got it from, internal documents. None of those were reviewed or relied upon by the experts, which is what I thought this was about, so we can talk about them, but they are not reliance materials there.

Second, the internal documents, you saw one, you may see others, a few points on them. Largely they are from 2019, when this was all kind of hypothesis generating and they are all fully consistent with the way science works. They identify issues, they look at existing data, and they say here we are going about this process. So, if you look at the end of the story and you pull the thread, what you will see are both internal and external documents that are fully consistent with the science outside the courtroom.

Just a word on dose, too. We have heard, kind of as advertised, that the vast majority of this presentation and

probably the next few days will be on NDMA, and your Honor is ultimately going to have to determine whether looking at Ranitidine data is more reliable than looking at all these other NDMA issues.

Genotoxin, you know, the point, we should put this in a bubble and no one should touch this because -- and these are my words, but the point is, this is so highly toxic that there is really no acceptable use. Well, you have also seen and you know from the data this is in cottage cheese, it's in beer, it's in charcuterie. Who kind of regulates all that? That is FDA. Has the FDA come out and said, oh, my gosh, this is a genotoxin, one drop, one molecule, if you have that cottage cheese you are at a higher risk of cancer? Of course not. This is why we look at the epidemiologic studies because, as I said earlier, our body is an incredible thing. We can get sick, we can get disease, but there are a lot of things that we are exposed to in cottage cheese, in charcuterie, in beer, that doesn't rise to the level of disease, and that is why these epi studies are so powerful, because they look at real world use.

With that, your Honor, thank you for your time.

*THE COURT:* Okay. Thank you all very much. That was a very productive morning.

That brings us to our lunch hour, so we have allotted an hour for lunch. We are about 15 minutes behind what we had anticipated, otherwise we are doing very well.

We have allotted 11:45 to 12:45, but we are closer to 12:00, so we will come back one o'clock and be ready to go into the Defense presentation.

You had allocated for the epidemiology motion 5699, we will push that back to one o'clock and otherwise try to follow the schedule as we had outlined.

The courtroom will remain open, so if you need to keep papers, that is fine. Have a good lunch and we will see you back at one o'clock.

(Thereupon, a luncheon recess was taken.)

* * *

*THE COURT:* Okay, you may be seated. Thank you.

All right. We now have the team presenting at what was 12:45, now 1:00 o'clock, the Defense first. It looks like you have several speakers. However you want to present the epidemiology motion at Docket Entry 5699.

You wanted a hundred minutes. You may proceed.

*MS. CANAAN:* Let me slide up. Perfect. Go to the next slide, please.

So, your Honor, I will be arguing the motion relating to Dr. McTiernan. Dr. McTiernan proffers the opinion that Zantac causes the five cancers at issue, and she proffers this opinion based on the weight of the evidence methodology.

So, to get to this opinion, Dr. McTiernan first considers the Ranitidine epidemiological studies, and she

concludes that they are largely not informative. She says they are largely not informative due to various methodological limitations. There is an issue, she claims, with low dose, duration of Ranitidine use, short followup, and exposure misclassification.

Because of these purported problems with Ranitidine studies, Dr. McTiernan said she had to extrapolate from epidemiological studies of dietary NDMA, of rubber workers, and studies of nitrite and nitrate that are potential precursors of NDMA to reach her conclusions about Ranitidine.

Also, to the extent that she considered any Ranitidine studies to be informative, Dr. McTiernan gave more weight to finding above 1.0 in the direction of an increased risk than to findings below 1.0 in the direction of a decreased risk, and finally, Dr. McTiernan interpreted all findings above 1.0 as an increased risk irrespective of their magnitude and statistical significance.

Next slide, please.

Your Honor, Dr. McTiernan's methodology is unreliable and inadmissible under Rule 702.

Although I have four reasons listed on the slide, and each one is independently sufficient to exclude Dr. McTiernan, there is a common theme here, your Honor. At every single step Dr. McTiernan's methodology was reverse engineered to get to a predetermined conclusion that Ranitidine increases the risk of

the five cancers.

To get to that conclusion she had to depart from well-established principles like statistical significance. She had to rely on studies that she previously rejected as unreliable. She had to cherry pick results across the epidemiological landscape, and she had to apply a glaringly inconsistent and irreconcilable methodology to the epidemiological data.

Next slide.

First of all, despite 14 large population based studies specifically examining the association between Ranitidine and the five cancers, Dr. McTiernan relied largely on non Ranitidine epidemiological data in reaching her conclusions.

Next slide.

In fact, as you can see, your Honor, she testified that she never even considered whether Ranitidine specifically was associated with any specific cancer type, and, your Honor, I have the word association underlined here because there is nothing wrong with considering other sources of data as part of a Bradford-Hill analysis if and when you get to a reliable association.

Earlier we heard Mr. Nigh say no reliable expert would ever exclude Hidajat, no reliable expert would ever exclude dietary studies from his or her analysis.

We are not saying that these other lines of evidence should be entirely excluded, that we should throw them out. We are saying you need to get a reliable association that is not due to chance and confounding before you get to Bradford-Hill. If you get to Bradford-Hill you can consider whatever lines of evidence you may see fit, but you I need to get to Bradford-Hill reliably.

To get to Bradford-Hill, you first need an association between the specific exposure and the specific outcome at issue, and that specific exposure here, your Honor, is Ranitidine.

Next slide, please.

Now, in her report, Dr. McTiernan reviewed four buckets of epidemiological data. She reviewed the Ranitidine studies, the dietary NDMA studies, the rubber industry studies, and studies lumping all nitrosamines, nitrites, and nitrates together.

She ultimately concluded that most of the Ranitidine studies were not informative with respect to the question of whether Ranitidine increases cancer risk.

Next slide, please.

*THE COURT:* Ms. Canaan, could you speak up a little bit into the microphone so everybody can hear you, including on Zoom. Thank you.

*MS. CANAAN:* Is this better, your Honor?

*THE COURT:* It is better for me, but it was fine for me to begin with, but there are others. We will let you know.

*MS. CANAAN:* Will do.

In fact, your Honor, just a few months ago Plaintiffs strenuously argued to this Court that Dr. McTiernan considered all, every single one of the Ranitidine studies to be completely uninformative and that therefore Defendants needed no additional time to cross-examine Dr. McTiernan about entirely uninformative studies.

Next slide, please.

So, while brushing aside most of the Ranitidine studies, Dr. McTiernan placed heavy reliance on dietary NDMA studies. Your Honor heard a great deal earlier today about the methodological limitations of dietary studies generally. Dr. McTiernan is certainly well aware of these issues. She is aware of these issues because she was a member of an advisory panel of experts at World Cancer Research Fund.

As we discussed at Science Day, your Honor, WCRF is a well respected worldwide organization whose mission is to review and synthesize research on the human diet and cancer risk. That is what they do.

What they do is they synthesize their conclusions into these monographs that relate to specific cancer types. Importantly, WCRF has issued monographs on each of the five cancers at issue in this litigation.

Next slide, please.

As you can see here, WCRF includes dietary NDMA in its 2016 stomach cancer monograph, and it is included under limited evidence, no conclusion, meaning that no conclusions about cancer risk can be reached. As you can also see, dietary NDMA is keeping company here with things like eggs, milk, coffee, and tea.

Next slide, please.

For all the other cancers, including esophageal, liver, pancreatic, and bladder, NDMA is not even mentioned, not at all.

That means that the data on dietary NDMA and these other cancer types were not sufficient to even warrant panel consideration of WCRF.

Next slide, please.

So, you may be wondering, your Honor, what did Dr. McTiernan, herself a former panel member of WCRF, have to say about this? Well, we asked her, of course, at her deposition, and Dr. McTiernan complained that WCRF has not updated their review of NDMA since 2005, but that, your Honor, is plainly contradicted by WCRF's 2015 systematic literature review on stomach cancer that, as you can see, clearly shows individual four core studies were considered as part of the 2015 review, yet absolutely no changes were made to the NDMA classification in the stomach cancer monograph.

Importantly, your Honor, there are no post 2015 dietary studies that Plaintiffs are relying on in this litigation on stomach cancer.

And so, the other thing that I want to point out about this, your Honor, as you can see, on top there it says number of publications RCTs/cohorts, and that is a really critical point, your Honor. In their systematic reviews, WCRF does not even consider, they don't even consider case control studies.

Next slide, please.

So, as your Honor may remember, case control studies start with cases, and these are people who have the disease, and then they compare them to controls, and those are people who don't have the disease, and typically cases and controls are then questioned about their past exposure. What did you eat, for example.

Now, unlike in case control studies, in cohort studies you start with people who are exposed and people who are not exposed, and then you follow them to see who will develop the disease and who will not develop the disease. The reason why this matters, your Honor, is that case control studies of cancer risk are notoriously prone to recall bias.

So, what is recall bias? Recall bias, simply put, means that patients are more likely to recall exposures that may explain their diagnosis. A cancer patient is more motivated to remember things that may explain why he or

she got cancer, and as a result, recall bias artificially inflates risk estimates in case control studies.

By contrast, in cohort studies recall bias is not an issue because exposure is determined before the person got the disease. That is the whole definition of a cohort study, the exposure is determine prospectively, not retrospectively.

Next slide, please.

Because of recall bias, WCRF explicitly states that they do not review -- they do not routinely review dietary case control studies, they don't even consider them.

Yet, contrary to the methodology that she applied as a panel member of WCRF, Dr. McTiernan relied on 39 dietary case control studies in this litigation as purported evidence of cancer risk.

Next slide, please.

Moreover, your Honor, Dr. McTiernan was the Plaintiffs' expert in the Talc and ovarian cancer litigation, and in that litigation Dr. McTiernan explicitly rejected dietary case control studies as reliable evidence of cancer risk. At the Daubert hearing at that litigation she testified, 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.

Next slide, please.

Similarly, at her deposition in the Talc litigation, Dr. McTiernan listed limitation after limitation after limitation of dietary case control studies that make them unsuitable for studying cancer risk. Let's listen to what she had to say.

"Nutrition variables are very difficult to ascertain for exposure because, as opposed to use of talcum powder products which might be used once or twice a day, nutrition variables are occurring sometimes 50 to a hundred times a day. The amount people eat, what they are eating, how often they are eating, the variables are so difficult to collect that they -- the results from case control studies are of concern to some investigators."

So, in the Talc litigation dietary case control studies are unreliable according to Dr. McTiernan, but in this litigation, virtually all the dietary studies that she relies on are in fact case control studies. There is simply no way to reconcile Dr. McTiernan's testimony in the Talc litigation and her opinions in this litigation.

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To be very clear, if she didn't rely on case control studies of dietary NDMA Dr. McTiernan would not be able to reach her conclusions that dietary NDMA increases cancer risk. For bladder, pancreas, liver, and esophagus there are no cohort studies showing a statistically significant increased risk in

any primary or overall analysis.

There is one study for esophageal cancer that finds one statistically significant increased risk in a sub group analysis, only in men, but again, no study for esophageal cancer overall shows an increased risk.

Similarly for stomach cancer, although there is one study, the Larsson study, that reports an increased risk, when all the cohort studies were added together in one analysis, including that Larsson study, there was absolutely no association.

So, if Dr. McTiernan applied the same methodology here that she applied as a panel member at WCRF, or the methodology that she advocated as a paid expert in the Talc litigation, your Honor, she could not have reached the conclusion that dietary NDMA increases cancer risk.

Next slide, please.

Now, Dr. McTiernan's extrapolation from the rubber industry studies is similarly problematic. In fact, Dr. McTiernan agrees that the dose and length of exposure in those studies may not have been accurately ascertained, if at all.

She also agrees that how inhaled NDMA may compare to NDMA ingested, such as with a Ranitidine tablet, is entirely outside her area of expertise.

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Finally, Dr. McTiernan's reliance on the nitrite and

nitrate studies contains even more logical leaps. By way of example, Dr. McTiernan relies on studies of nitrate levels in municipal water and cancer risk. In essence, what she is saying is this: These studies are relevant because once ingested, some of the nitrates may convert to nitrites, and then some of the nitrites will then form nitrosamines. By the way, your Honor, there are over 300 nitrosamines, they are all different.

She says, one of those nitrosamines may be NDMA. It is an assumption stacked upon assumption stacked upon assumption.

Next slide.

So, your Honor, I submit that Dr. McTiernan's extrapolation from these studies of nitrates, of nitrites, of all of those combined, not to mention rubber workers in England, is a quintessential example of what the Joiner Court called simply too great an analytical gap between the data and the opinions proffered.

Next slide.

Now, in addition to embracing the dietary rubber worker and nitrate studies, Dr. McTiernan also improperly discounts the Ranitidine studies, and in particular, the active comparator analyses that Mr. Cheffo addressed earlier that compare Ranitidine to other acid suppressing drugs like PPIs and H2 blockers.

Next slide, please.

Now, reportedly Dr. McTiernan has used active comparators in her own studies of medications and cancer risk, and she agrees in her report that active comparator analyses are a strength over Ranitidine studies because they control for confounding by indication.

Next slide.

In fact, your Honor, we can readily see how active comparators control for confounding in Ranitidine studies. What you have in front of you is a forest plot of the results from studies that compared Ranitidine to the general population of nonusers of any acid suppressants, and you can see that most of the risk estimates are to the right of 1, in the direction of an increased risk.

Now, if we compare this forest plot to the results that we have from active comparator Ranitidine studies --

Next slide, please.

-- your Honor, you can plainly see that all the risk estimates shift to the left, in the direction of no association or a decreased risk.

Next slide, please.

Now, Dr. McTiernan discounted the Ranitidine active comparator studies for the following four reasons: First, she says PPIs and other H2RAs, they also increase the risk of cancer, so any increased risk for Ranitidine in analyses

comparing Ranitidine to these other drugs will be obscured.

Second, she says Famotidine users, they are not a good comparator, they are too different from the Ranitidine users.

Third, she says the doses and durations of Ranitidine were insufficient to cause cancer, they were too low.

Fourth, she says followup was not long enough to allow for other cancers to develop, and as you will see, your Honor, there is simply no factual basis for any of these claims.

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First, at her deposition Dr. McTiernan walked back her claim that PPIs increase cancer risk. In fact, she could not name a single cancer that PPI use was even associated with, much less causally associated with.

Next slide.

Second, at her deposition, she also walked back her opinion that other H2 blockers increased cancer risk, testifying unequivocally, no, it is not my opinion.

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Third, Dr. McTiernan claims that Famotidine users are different from Ranitidine users, and that therefore, she says, a general population or a nonuser comparator is better. For example, with respect to the Mohy-ud-din study, this is what she writes in her report, Ranitidine and Famotidine differ substantially in many ways that are related to cancer, and she actually faults the investigators for not presenting the

analysis of Ranitidine users versus the general population.

This claim, your Honor, is objectively contradicted by the data. As you can see on the right side both Ranitidine -- and these are baseline characteristics directly lifted from the Mohy-ud-din in abstract.

Both Ranitidine and Famotidine users were almost three times more likely to smoke than the general population. Both Ranitidine and Famotidine users were more than five times more likely to be obese than the general population, and they were more than three times more likely to use alcohol than the general population.

Of course, we all know that smoking and obesity and alcohol are well established risk factors for cancer.

So, this is exactly, exactly why active comparators are key to controlling for confounding in studies of acid suppressants like Ranitidine and cancer risk, and exactly why every recent study, every investigator designed their study with an active comparator design.

I will submit, your Honor, that for an expert to look at this data from the Mohy-ud-din abstract and to say that the general population comparator is a better comparator than Famotidine, I will submit that is the mark of an advocate for a cause.

Next slide, please.

Another criticism that Dr. McTiernan has of the

Ranitidine studies is that the patients were not followed long enough after exposure to Ranitidine to develop cancer, but at her deposition she couldn't tell me how long the followup must be to detect any particular cancer after Ranitidine exposure.

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And although in her report Dr. McTiernan claims that for a rare end point like cancer, folks must be followed for decades. In her own peer reviewed studies of medication and cancer risk, she didn't follow folks for decades. In fact, most of the time she followed folks a fewer number of years than the Ranitidine study followup that Mr. Cheffo addressed earlier today.

Next slide.

Moreover, Dr. McTiernan's speculation that longer followup would reveal increased cancer risk is objectively, objectively contradicted by the data, your Honor. From Iwagami to Kantor, to Norgaard, Ranitidine study authors specifically considered this issue, and they determined that longer followup did not lead to an increased risk of cancer.

On the forest plot, orange lines represent shorter followup, blue lines represent longer followup. For bladder cancer, for example, as you can see, your Honor, longer followup of more than ten years did not increase cancer risk.

In fact, in most cases, longer followup moved risk estimates to the left in the direction of a decreased risk.

Next slide, please.

And lastly, Dr. McTiernan speculated that the dose or duration of Ranitidine use were insufficient to cause cancer, but again, when pressed at her deposition, she acknowledged that she doesn't have an opinion about what dose or what duration of Ranitidine will show an increased risk.

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And again, Dr. McTiernan's speculation that higher doses or longer durations may lead to an increased risk of cancer, it is squarely contradicted by the data.

Here again orange lines represent lower dose and duration while the blue lines represent higher dose and duration. As you can see, in most instances, higher dose or duration of Ranitidine use moved risk estimates to the left in the direction of a decreased risk.

The only time you really see a stark differences is for esophageal cancer, all the way on top. You can see that low dose of Ranitidine was associated with an increased risk because the dose was not high enough to protect from GERD, while higher doses of Ranitidine were associated with a strong protective effect.

You know, earlier we heard from Mr. Nigh that the Adami study purportedly showed dose response. I will submit, your Honor, objectively looking at this data from the Adami study, it is not possible, it is not scientifically possible to

draw that conclusion.

Next slide, please.

And in case there is any doubt as to what actual true dose and duration response actually look like, this is a forest plot showing how increasing dose and duration of smoking relates to the risk of bladder cancer.

As you can see, your Honor, with every incremental increase in dose or duration there is a reliable and consistent movement of risk estimates toward the right in the direction of an increased risk.

So, the bottom line here is this: Dr. McTiernan's criticism of the Ranitidine studies, from active controls, to dose and duration, to length of followup, they are objectively contradicted by the Ranitidine data. They have no reliable basis in fact.

Next slide, please.

Dr. McTiernan's third methodological flaw is that, by her own admission, she assigned greater weight to study results that favored her conclusion.

Next slide, please.

In fact, in her expert report Dr. McTiernan specifically states that because of the purported bias toward the null in the Ranitidine epidemiological studies, she gave less weight to the relative risks that were not greater than 1, and put more weight on relative risks that were greater than 1.

In other words, she put more weight on positive findings in the direction of an increased risk and she discounted negative findings in the direction of a decreased risk.

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Your Honor, I will submit there is no epidemiology test in the world that supports this quintessentially result driven weight methodology. It is not surprising, your Honor, when scientists reliably and impartially consider epidemiological literature, they don't say this is a bad study, but gee, I will cherry pick out the results that are in the direction of an increased risk. Nobody does that.

If it is a bad study, then you either don't consider it or you give the entire study less weight in your assessment. What you don't do is, you don't pick out the risk estimates that you like and give them more weight.

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As another Court put it, under certain circumstances, it is not scientifically reliable to generally attack epidemiological studies as fundamentally flawed while at the same time selectively plucking favorable numbers that are not statistically significant, yet that is exactly what Dr. McTiernan did here.

Next slide, please.

Moreover, Dr. McTiernan's basis for giving more weight

to relative risks above 1.0 is this purported bias towards the null from misclassification of Ranitidine exposure.

I will demonstrate, your Honor, that like other criticisms of the Ranitidine studies, this criticism also has no basis in fact.

Next slide, please.

So, I want to start first by explaining Dr. McTiernan's argument about misclassification bias.

So, most, although not all, your Honor, not all -- there are some studies of Ranitidine that look -- specifically look at over-the-counter use, but most of the studies, Ranitidine studies, are cohort studies that compare people who are exposed to prescription Ranitidine to people who are not exposed to prescription Ranitidine.

So, Dr. McTiernan posits that some of these folks in the not exposed group may have been exposed to over-the-counter Ranitidine, and investigators didn't encounter that.

She the posits that if a sufficiently high number of these over-the-counter users are included in unexposed controls, and if Ranitidine in fact increased the risk of cancer, then these over-the-counter users could have diluted, they could have obscured the observed association, and so the Ranitidine studies could have therefore underestimated the actual true risk. That is her argument.

Next slide, please.

Now, there are numerous problems with Dr. McTiernan's assessment of purported misclassification. I am only going to focus today on the top four issues of her assessment.

Next slide, please.

First of all, Dr. McTiernan speculates, she speculates that misclassification occurred in the first place. In her deposition she conceded that she cannot say that even a single person was definitively misclassified in any Ranitidine study.

Next slide, please.

Second, Dr. McTiernan never attempted to estimate the magnitude, right, the magnitude of any bias from purported misclassification of exposure in Ranitidine studies. By contrast, Defendants' epidemiologist, Dr. Andrew Chen, concluded that even if up to 90 percent of over-the-counter Ranitidine use was misclassified in these Ranitidine studies, this would have a very small effect on the risk estimates.

Next slide, please.

Third, Dr. McTiernan admits that all biases have to be considered when interpreting study results. That is a critical point, your Honor.

Next slide, please.

She also admits that in the Ranitidine studies protopathic bias, also known as reverse causation, and confounding by indication tend to result in spurious and false

increased risks, and the study authors say the same thing. For example, the Adami authors wrote that potential confounding by indication reverse causality favors spurious positive associations.

Next slide, please.

And yet, while Dr. McTiernan claims 34, no less than 34 separate times in her report that misclassification of exposure underestimated risk in Ranitidine studies, she never, not once, states that other biases could have over estimated risk, and this despite her admission that you have to consider the combined effect of all the biases.

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Lastly, but perhaps most importantly, Ranitidine study authors considered this issue, they considered the possibility of misclassification of exposure due to over-the-counter Ranitidine use, and these study authors concluded that the active comparator analyses minimize the likelihood of any resulting bias.

For example, the Adami authors wrote that the magnitude of any bias would be limited in the comparison between users of Ranitidine and other H2RAs. The Norgaard study authors wrote we would expect concomitant use of over-the-counter Ranitidine to be low.

By the way, there was a claim made earlier about the Norgaard study authors being purportedly biased, and I will

submit, your Honor, that the basis for the claim, frankly, appears to be just the fact that some of these study authors coauthored a study earlier with Drs. Adami and Chang. There is really no reliable, much less scientific basis for this claim.

So, for all these reasons, your Honor, Dr. McTiernan's claims, the purported misclassification of over-the-counter Ranitidine use under estimated cancer risk, it has no basis in fact, and it is contradicted by the Ranitidine study authors.

That is yet another reason why Dr, McTiernan's methodology that gives more weight to positive findings than to negative findings is completely unreliable and inadmissible, your Honor.

Next slide, please.

Dr. McTiernan's fourth critical methodological failing is that she disregarded statistical significance and applied an inconsistent and litigation driven methodology.

Next slide, please.

In her report Dr. McTiernan states that every relative risk other than 1.0 indicates an association, irrespective of its magnitude or statistical significance. Dr. McTiernan's definition of association conflicts with the Reference Manual on Scientific Evidence that explicitly incorporates the concept of statistical significance into its definition. The reference manual says more or less frequently than one would expect by chance alone.

Now, Dr. McTiernan's definition of association is also at odds with Dr. Moorman's concession that when there is no association between an exposure and an outcome, one would expect to see risk estimates clustered around 1, with some estimates greater than 1 and some less than 1.

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Moreover, Dr. McTiernan's definition of association is also patently litigation driven. As you can see here, your Honor, in her Zantac report a non-statistically significant relevant risk of 1.5 or 1.6 is described as an increased risk, but in her Talc report a non-statistically significant relative risk of 1.4 is described as no association, and in her published peer reviewed studies, even a borderline statistically significant finding like you can see on the bottom of 1.6 with a lower confidence interval of 1.0 is a borderline statistically significant increased risk.

She still calls it no association because that 1.0 overlaps, that confidence interval overlaps the line of unity. So, there is absolutely no consistency here, your Honor.

Next slide, please.

Indeed, in her deposition, Dr. McTiernan did not even attempt to explain why a relative risk of 1.06 was an increased risk in her Zantac report, but a relative risk of 1.4 was no association in her Talc report.

Next slide, please.

Even more importantly, your Honor, Dr. McTiernan applies her definition of association inconsistently to the data that supports and does not support her opinion.

For example, in her Zantac report she claims that any relative risk other than 1.0 indicates an association, whether positive or negative, but in the same report, when she discusses a Ranitidine study with a relative risk below 1.0 in the direction of a decreased risk now, she calls it no association.

So, for Ranitidine above 1 is an increased risk, but below 1 is not an increased risk. This is a quintessentially result driven and unreliable methodology.

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In fact, your Honor, there are 80 separate risk estimates below 1.0 in the Ranitidine epidemiological studies that specifically relate to the five alleged cancers, 80 risk estimates, yet not once does Dr. McTiernan describe them as a decreased risk. By contrast, virtually every single risk estimate above 1.0, even a 1.05 and a 1.06 is described as an a increased risk.

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And there are many other examples of Dr. McTiernan's inconsistent methodology. For example, she rejects the Iwagami study, which of course finds no increased risk of cancer with Ranitidine, and she rejects it because she says combining

Ranitidine and Nizatidine users into one group is highly problematic. She says it is highly problematic because you are not seeing the specific effects of Ranitidine, yet at the same time she embraces studies of all nitrosamines combined.

As I mentioned earlier, there are more than 300 different nitrosamines, only one of which is NDMA. She embraces studies of processed meats that she admits contain many different nitrosamines, in addition to numerous known carcinogenic chemicals, like polycyclic aromatic hydrocarbons for example, so group one carcinogens.

She embraces studies of nitrite and nitrate, which she admits may or may not form nitrosamines which may or may not be NDMA. Again, your Honor, there is absolutely no consistent methodology here.

Next slide, please.

Similarly, Dr. McTiernan rejects Zantac's study analyses that lump all the different cancer types together, and these also happen to be the analyses that find no increased risk, and she rejects them because she says you have to look at the individual cancers.

We agree with that, your Honor, you have to look at the individual cancers, yet in the same breath, she relies on NDMA studies that lump all cancers together and extrapolates form these studies -- from these results that NDMA increases the risk of all cancer. Again, this a completely

irreconcilable and inconsistent methodology.

Next slide.

And here is another example. Dr. McTiernan stated in her report that crude or unadjusted, meaning -- by not adjusted meaning not adjusted for any confounding variables. She says crude relative risks could be confounded and therefore are not informative. That makes sense. And yet, after she learned at her deposition that she erroneously reported and relied on elevated crude risk estimates from the Adami study, Dr. McTiernan changed her tune and she decided that she can rely on raw or crude data for her opinions.

By contrast, Dr. Moorman, Plaintiffs other epidemiologist, reported the correct adjusted risk estimates from the Adami study, and she does not rely on the crude data from the Adami study that Dr. McTiernan relies on.

Next slide, please.

Now, Courts and scientific authorities are in accord that reliance on non-statistically significant data, on lumped exposure data, on lumped outcome data, on crude data, these are all red flags, these are all indicia of an unreliable methodology. But I will submit, your Honor, that even more compelling in Dr. McTiernan's case is that she employs these methodologies situationally, depending on whether or not they advance her bottom line.

She interprets non-significant risk estimates above 1

as an increased risk, but does not interpret those below 1 as a decreased risk. She rejects lumped exposure and outcome data when it is not helpful, but she relies on it when it is helpful.

She rejects crude data, saying it is confounded, that is what she says in her report, but once she realized that she mistakenly included all the crude risk estimates from the Adami study in her report, she pivots and now she says it is totally fine to rely on crude data.

Next slide, please.

That is the one glaring, overarching, underlying methodological flaw in Dr. McTiernan's methodology. Mr. Cheffo referred to it earlier, it is situational science. Simply put, Dr. McTiernan applies whatever method is expedient to get to her desired conclusion. That is the antithesis of reliable science, your Honor. It has no place in the courtroom and it must be excluded.

Thank you, your Honor.

*THE COURT:* Okay, thank you very much. That was about 45 minutes. Now we are going to hear on Dr. Moorman.

*MR. BROWN:* Your Honor, I am Loren Brown, I am arguing the motion to exclude Dr. Moorman.

*THE COURT:* Good afternoon.

*MR. BROWN:* Okay. Let's pull up the slide deck.

Your Honor, I guess it would make sense to start with

Dr. Moorman's general causation opinions. You know the five cancers at issue by now, so I don't need to belabor that. As you also know, Dr. Moorman decided not to render causation opinions on four other cancers that she actually analyzed, and I will briefly touch on that in a minute, but before I do that, I want to give you a brief outline of my points today.

Next slide, please.

So, your Honor, we have divided this into three parts. This probably sounds familiar already, but we are going to talk in the first part about the association part of Dr. Moorman's analysis, and we are going to break that into two groups. The first group is going to be her evaluation of the Ranitidine studies, and why that was improper and unreliable. Then I will focus mostly on the dietary studies. I know it says occupational studies here, but in the interest of time, I will try to cut through that and talk about her reliance on the dietary studies, and why that wasn't reliable.

Then we are going to talk about Dr. Moorman's Bradford-Hill analysis and some of the key components of that. We are not going to go through every factor, but three of the relevant components we will talk about, and if, and only if I have time either now or in any rebuttal, we will talk about the general acceptance factor as applied to Dr. Moorman.

The reason why I have singled that out for Dr. Moorman is because Dr. Moorman, as you will see in her report and in

her work in the record that we have submitted, puts a lot of emphasis on the whole principle of general acceptance, and we have cites to that in the record.

Next slide, please.

So, with that, your Honor, I would like to turn to the analysis that purportedly supports Dr. Moorman's general causation opinions.

In this case, as you can see by now, I point out first that the steps that need to be taken in a case like this appear to be undisputed. As we can see here in the reference manual, there is no dispute that the first step is to review the available studies to determine whether there are alternative explanations for any apparent association or observed difference, namely alternative explanations such as bias and confounding.

There is also no dispute about the second step, and that is to consider how guidelines for inferring causation from an association applied to the available evidence. The guidelines Dr. Moorman used here, as you have heard already, are the Bradford-Hill criteria, which are fine, though we obviously have problems with how she applied the criteria in this case.

I am going to start by spending some time on the way that Dr. Moorman applied step one, and in particular, the method she used to weight the epidemiological data before

concluding that there is a valid association between Ranitidine use and all five cancers now at issue.

Next slide.

I thought it would be helpful to talk about Dr. Moorman's analysis of the Ranitidine studies in three parts.

The first part is her analysis of these active comparator studies, and why that was improper and why it is unreliable. Then we are going to talk about the heavy reliance that she placed on the nonuser studies, putting them above all other studies, and why that was improper and unreliable.

And then I want to say a few words about the weighting criteria that she used and picked and how she applied those criteria and the standards or lack of standards that she used in doing that.

Next slide, please.

Now, your Honor, we received the first indication of a process without appropriate standards very early in Dr. Moorman's deposition when we asked her about the main evidence or factors that distinguished the five designated cancers from the other four.

As you can see here, Dr. Moorman's opinion regarding the other four cancers, which is on the left taken directly from her expert report, but as you can see on the right, when we asked her to identify any factor, any factor at all, and I asked her this a few different ways, that distinguish the five

designated cancers from the other four she evaluated, she could not identify anything other than to say the five cancers have the strongest evidence.

Now, that was just the first red flag that came to our attention. I know Mr. Nigh provided an explanation on why they are pursuing five over the other four this morning, but that is not what Dr. Moorman said at all.

Next slide, please.

Now, let's talk about Dr. Moorman's weighting of the studies for all five cancers at issue, your Honor. We constructed this chart based on how Dr. Moorman weighted all the observational studies in her report. She confirmed all of these designations in her deposition.

As you can see here, Dr. Moorman strongly weighted only four studies, all of which compared Ranitidine users to nonusers, and all of which came from what we have been calling the Scottish database.

And then below these studies, in her hierarchy, Dr. Moorman moderately weighted four dietary studies and one occupational study. Then finally, at the bottom of her hierarchy, those studies receiving the lowest weight reflected here on the right, she put all the active comparator studies that were specifically designed to evaluate the Ranitidine and NDMA question after 2019, when the issue arose.

She also gave little or very little weight to three

nonuser studies, Habel, Tran, and Kim, even though Plaintiffs' counsel referenced their studies earlier today.

One additional note, your Honor, relates to the Cardwell study you have heard a lot about already. While Dr. Moorman weighted the nonuser part of the Cardwell study, which you see on the left, that study also included an active comparator analysis.

Dr. Moorman did not rely on the active comparator analysis in Cardwell, and as we'll discuss in a few minutes, she has significant problems with active comparator analyses in all of these Ranitidine studies. For Cardwell, she did not even include the H2RA active comparator results in the data summary that is part of her expert report.

So, your Honor, you know by now the result of grouping the Ranitidine studies this way, the active comparator studies would show no evidence of an increased cancer risk for any of the five cancers, more or less get put to the side.

The nonuser dietary and occupational studies, which do contain some statistically significant results for some of the five cancers, become the most significant part of Dr. Moorman's foundation.

We don't believe this was a product of a reliable methodology, your Honor, and now I am going to try to explain why.

Let's go to the next slide.

So, first, I am probably not going out on a limb when I say that the most significant issue to resolve on this motion is whether it was reliable for Dr. Moorman to reject the active comparator analyses in favor of the nonuser analyses, the dietary studies, and the occupational studies. That is why it is point one in this outline.

Next slide.

Now, before I address the specific foundational problems with Dr. Moorman's analysis of these Ranitidine observational studies, I think it makes sense to briefly review some of the core undisputed principles that relate to observational studies generally.

As you know by now, this case does not involve randomized clinical trials in which the groups being compared are well matched at baseline; instead, all the experts in this case are operating in a much more challenging world of observational studies where the reliability of the study data rises and falls on the similarity of the groups being compared at baseline.

With the exception of the medication of interest being given to one group, researchers want to get as close as they can to what Mr. Cheffo described as an apples to apples comparison at baseline. The further we get away from apples to apples, the bigger the confounding problem. That is the potential that a difference observed at the end of the study is

due to population differences that existed from the start rather than due to an effect of the medication being studied.

Here you can see the numerous statements in the reference manual about the significance of confounding in any case that turns on observational data like this one.

Next slide.

And so, when a researcher finds an association between a medication and a disease, like Dr. Moorman purportedly did by rejecting the active comparator studies and instead relying on the Ranitidine nonuser studies, it is methodologically critical to determine whether the association is valid as opposed to being the result of confounding.

Next slide.

Now, in her expert report, Dr. Moorman says that she addressed confounding, but before we get into that I think we need to be clear when we talk about confounding in this case because we have two major types that we need to be mindful of when we evaluate whether it was valid for Dr. Moorman to put all the active comparator studies at the bottom of her pile in favor of other studies, including the dietary and occupational studies.

So, what you see here is a Venn diagram that shows the cancer risk factors that can confound any analysis of Ranitidine users. Certainly these include conditions that patients take Ranitidine for, that is conditions that

Ranitidine is designed to treat, and that also increase the risk of many cancers.

As you have heard many times already, these are called confounders by indication and Dr. Moorman acknowledges these confounders at least for certain of the cancers, gastric, esophageal, and she says possibly liver cancer.

The other important group of risk factors, though, relate to conditions of lifestyle choices that a patient doesn't necessarily take Ranitidine for, but which are more common in Ranitidine users and nonusers, and which can also confound an analysis.

Smoking is a good example, and Ms. Canaan made reference to that a few minutes ago. Smoking can contribute to reflux disease and it increases the risk of almost all types of cancer, but patients do not take Ranitidine to treat their smoking. These are residual confounders, and it is equally important to be able to control for them in any analysis.

If information about these factors isn't available in a database, you obviously can't control for them and confidently rule out residual confounding as the explanation for any observed difference, especially whereas here the observed differences are very small. As you will see in a few minutes, that is a big issue.

Next slide, please.

Now, both types of confounding are well-recognized

challenges for researchers trying to determine whether a particular medication increases the risk of certain types of cancer, and that is why the scientific community universally recognizes that active comparator designs are the best designs to address these challenges. As you can see here, even Dr. Moorman agrees with this principle, at least in general and at least with respect to confounding by indication.

Now, both types of confounding are critical in the validity of Dr. Moorman's rejection of the active comparator studies, as well as her heavy reliance on the nonuser studies.

Next slide, please.

So, what is Dr. Moorman's stated basis for rejecting the active comparator analyses in favor of nonuser analyses, dietary studies, and occupational studies in this case?

Well, she claims that the active comparator studies are appropriate only when two assumptions are met, namely, that the comparator drug is not associated with the outcome of interest, here five different kinds of cancer, and that the two medications being compared are used to treat similar conditions.

Here, however, she argues that neither of these assumptions are met, and that is why she does not accept the active comparator results in this case, and at least part of why she gave these studies little or very little weight in her analysis.

So, now I want to talk about each assumption that Dr. Moorman claims is unmet.

Next slide, please.

Your Honor, here is why Dr. Moorman says neither assumption is met. First she claims that other H2RAs which have not been linked to NDMA still cause the same cancers for other reasons; and second, that patients who take other H2RAs are different and I guess sicker than patients who take Ranitidine.

For these reasons she claims that active comparator analyses are inappropriate in this case and mask a cancer risk that is associated with the use of Ranitidine.

Next slide.

So, moving to the first point, Dr. Moorman went and found some studies in the literature which allegedly showed that other H2RAs can increase the risk of certain cancers.

Just to give us a background on this, she cited five studies. Those five studies looked only at gastric, pancreatic, and liver cancer, not the other two. None looked at bladder or esophageal cancer.

Moreover, as you can see on the right, two of those five looked only at the cancer risks of PPIs, not other H2RAs, and that is why we have red lines crossing out those studies, and of the three studies that did look at other H2RAs, one, Lin, as you can see on the right, found that they had a

protective effect.

Another, Laoveeravat, found no association after the authors excluded a study with the most extreme results, and the last one on the list here is a little more complicated. It was a meta analysis where the authors ranked these studies according to their quality. The only study that was ranked by the authors as having a high quality reported that the association was probably not causal, and most likely due to confounding by indication.

So, this was the foundation for that opinion.

If we could go to the next slide, please. Next slide, please.

More significantly, your Honor, when we asked Dr. Moorman questions about her contention that other H2RAs are improper comparators, she made a number of significant admissions.

First, she admitted that she didn't really do a full causal analysis of that claim or do a Bradford-Hill analysis of any kind, that is on whether other H2RAs caused these cancers. She admitted that she has never shared this view outside of this litigation, peer reviewed or otherwise.

She did not recall whether FDA approved labels for any of the other H2RAs warn of an increased cancer risk. They don't.

She is not aware of whether FDA, IARC, or the American

Cancer Society, or any other institution has concluded that other H2RAs increase cancer risk. They haven't.

She couldn't name any medical guidelines that suggest patients should stop taking H2RAs because of increased cancer risks. There simply aren't any.

This claim has no reliable basis or support outside of this litigation, and it is a foundational pillar of Dr. Moorman's decision to reject the active comparator analyses. Throughout her report and in contrast to what the Plaintiffs say in their briefs, this is Dr. Moorman's first and foremost reason for rejecting all the active comparator analyses in her report.

Next slide, please.

The second claim, as you see here at the bottom of this slide, is equally unreliable. Here Dr. Moorman cited one study, Kim, the same study that Mr. Nigh spent about 15 minutes criticizing, to support her claim that Ranitidine users are significantly different from users of other medications in the same class.

To support this claim Dr. Moorman cites one study to which she assigns low weight overall in her own report, and even Dr. Moorman admits in other parts of her report and in her deposition that one study doesn't reliably establish anything.

Moreover, other researchers, such as Dr. Iwagami, have criticized Dr. Kim's method of evaluating these differences,

probably for the same reasons that -- or at least some of the reasons that Mr. Nigh was criticizing Kim. Mr. Nigh described the study that Dr. Moorman relied on to establish these differences as an outlier and unreliable, and he said there was something terribly wrong with Kim's database.

That is the foundation for the second claim.

If we could go to the next slide, please.

More importantly I'd say, nobody else in the medical, scientific, or regulatory communities have said that active comparator studies are problematic because of meaningful differences in these populations, let alone more problematic than nonuser, dietary, and occupational studies.

Nobody has suggested the differences between Ranitidine users and other H2RA users are masking a cancer risk associated with Ranitidine use. Indeed, researcher after researcher, as you can see, explain that they chose active comparators to reduce confounding and to minimize population differences at baseline.

As you heard from Mr. Petrosinelli, as a matter of law taking positions that are in such conflict with the authors themselves is another major red flag under Daubert.

So, the two major reasons why Dr. Moorman found active comparator analyses to be invalid are themselves flawed and not based on a reliable evidentiary foundation.

Next slide, please.

So, let's talk about the reliability problems associated with Dr. Moorman's analysis of the nonuser studies.

Next slide.

I guess I will start with what is undisputed. First, your Honor, there is no dispute that each of these five cancers have risk factors or confounders that need to be controlled for in the analyses.

Next slide.

As you can see in this slide, there is also no dispute that the failure to control for these risk factors due to missing or incomplete information could result in an over estimate of the risk, particularly if the exposed group, meaning the group taking Ranitidine, has a higher prevalence of some of the risk factors.

We asked Dr. Moorman about this in her deposition and she conceded that if the exposed group had a higher prevalence of some of the risk factors than the unexposed group, then failure to control for that could result in an over estimate of the relative risks.

Next slide, please.

Now, things start to become disputed when we are talking about whether the nonuser studies that Dr. Moorman heavily weights were able to control for key risk factors.

On the left you can see that Dr. Moorman suggests that these authors did adjust for these confounders, but on the

right you can see that the authors themselves acknowledged that they still could not control for a number of key risk factors due to missing information, and as a result, they could not rule out confounding as an explanation for their results.

You can see in Cardwell acknowledging that he was unable to control for several bladder cancer risk factors. In Tran, the main limitation is that we cannot control or rule out confounding. In Liu, we are not able to adjust for H. pylori, an important risk factor for gastric cancer.

Next slide, please.

Now, in this next slide, your Honor, you see a chart that illustrates the key risk factors that could not be controlled for in Dr. Moorman's heavily weighted studies. The information supporting this chart was taken directly from the publications.

The red boxes identify risk factors for which there was no information in the study database. The yellow boxes identify risk factors for which the information was limited. The point is that the major risk factors could not be controlled for nonuser analyses, and the authors acknowledge the baseline imbalances in these groups could easily explain small differences that they observed. Dr. Moorman just looked past these significant limitations and acknowledgments by the authors.

Next slide.

Mr. Petrosinelli already mentioned the case law here within the Eleventh Circuit showing that experts cannot exceed limitations imposed by study authors, and that being one reason why Courts exclude experts in this circuit.

Next slide, please.

Now, your Honor, I want to spend a few minutes talking about some of the other criteria that Dr. Moorman said she weighted heavily and that support her view that nonuser studies, dietary studies, and occupational studies are superior to the active comparator studies.

Next slide.

Now, as can you see on this slide, Dr. Moorman says that she gave greater weight to three criteria. Your Honor has asked about some of this in the questions leading up to the hearing. So, first, how did Dr. Moorman decide that these criteria should get the greatest weight and how did she apply them to the Ranitidine study data?

Next slide.

Now, in her academic career, Dr. Moorman often used established peer reviewed scales to weight epidemiological studies. In fact, some of the studies that she cited in her report used these established scales that I just mentioned. Here, instead Dr. Moorman used what she described as her own qualitative judgment or qualitative rating of the studies.

I am going to now talk for a few minutes about these

criteria and how they were defined and applied here.

Next slide, please.

So, let's start with followup time.

We started by asking Dr. Moorman to tell us what adequate followup time would be in this context. She couldn't tell us what duration of followup would be adequate in her opinion, and instead said that it is a continuum, and you see that here.

Next slide, please.

When you look at followup time on a continuum, at least objectively, it would be impossible to rationalize why all the active comparator studies are at the bottom of Dr. Moorman's pile, even below dietary and occupational studies, and why certain nonuser studies are at the top.

In this chart, for example, you can see that some of the active comparator studies shaded blue, Norgaard and Adami in particular, have longer durations of followup than all the nonuser studies Dr. Moorman relies on, and there certainly is no pattern that could support Dr. Moorman's weighting decisions based on followup time.

Next slide, please.

Let's now talk about sample size.

We have the same problem with sample size. We asked Dr. Moorman to tell us what constitutes an adequate sample size in this context, and again she refused to give a number or

range and instead said it is on a continuum.

Next slide.

Now, when you look at the studies organized by sample size, namely by the number of cancers in the study, again, there is no pattern that would support a decision to give all the active comparator analyses little or very little weight and to give nonuser studies heavy weight.

I know this slide is busy, but what we tried to do is plot the studies by sample size for each of the five cancers.

The nonuser studies that Dr. Moorman assigned heavy weight to are highlighted with orange dots next to them, and you can see that many of the active comparator studies that Dr. Moorman put at the bottom of her weighting scale have larger sample sizes than the nonuser studies she weights heavily.

Now, I realize that Cardwell has the largest sample of cases for bladder cancer, but it is important to note again that Cardwell also has an active comparator analysis, and Dr. Moorman rejects all the active comparator analyses for the reasons we have previously discussed.

Next slide.

So, the last of Dr. Moorman's three heaviest weighted criteria that I would like to talk about is ascertainment of exposure, or put a different way, misclassification of exposure. Ms. Canaan spoke about this in the context of Dr. McTiernan.

As I'm sure you know by now, Dr. Moorman also claims that unmeasured use of OTC Ranitidine somehow contaminated these studies and obscured an increased cancer risk that we can't see in the relative risk estimates that we have in these studies.

We believe this claim is pure speculation and not supported by any actual data from the studies, and that response applies both with respect to the amount of misclassification in any group of any study and the impact that any alleged misclassification had on the risk estimates.

Here, as you can see, Dr. Moorman concedes she is unable to quantify either the amount of misclassification in any group in any study, or the impact that such misclassification had on the results.

Next slide.

Yet another red flag on this misclassification issue relates to the positions Dr. Moorman takes regarding certain studies in particular. For example, while she claims that misclassification of exposure is of particular concern in the Adami and Norgaard studies, the researchers in these studies specifically considered this issue and concluded that any misclassification due to OTC use was limited, and that it would not affect the results.

Dr. Moorman not only failed to provide data to support her claims about misclassification, but the authors themselves

analyzed the issue based on their own data and reached an opposite conclusion. And again, Mr. Petrosinelli mentioned the cases, McClain and Accutane, in which experts have been excluded for, among other reasons, interpreting data in ways that conflict with the study authors' interpretations of their own data.

Next slide, please.

I think it is also important to point out that no other researcher or in the peer reviewed medical community has suggested that the study results Dr. Moorman diminishes are invalid due to a misclassification or an exposure problem.

Here we asked Dr. Moorman to name any, any that she could not -- any that has said that, and she could not do that. In the interest of time, I am not going to read the whole quote, but you can see in the answer she is not recalling anyone who claims that misclassification of exposure had an impact on the point estimates, P values, or confidence intervals that were reported in those studies.

Next slide, please. Let's go to the next slide, please.

Now, just in case Plaintiffs say we are looking at each of these factors in a vacuum, we thought it would be helpful to provide a couple of examples that combine all three of these factors so you could see just how inconsistent the data are with Dr. Moorman's weighting decisions.

The first example on the left is a pancreatic cancer example comparing Adami, which Dr. Moorman weights as low, meaning below dietary and occupational studies, and McDowell, which Dr. Moorman weights strongly. Adami has a longer followup and much longer sample of cases than McDowell. Both these studies use prescription drug databases in which OTC use can't be measured.

Again, based on application of these factors, it would be impossible to rationalize how Adami receives little weight and McDowell receives heavy weight according to these factors. This is further evidence of an inherently unreliable process.

The bladder cancer example on the right highlights the same problem, but in the interest of time, I will leave this for the Court's consideration and move to Dr. Moorman's reliance on the dietary studies.

Next slide.

Now, on these dietary studies, I am going to make three points, your Honor. The first is, while the Plaintiffs claim that these dietary studies fill a gap in the Ranitidine data, we don't believe that is true. The dietary studies are not any more informative on the key parameters that we have been talking about than the Ranitidine studies, and I will talk about that.

The second point is that the dietary studies do not reliably correlate NDMA levels with the five cancers. Most of

these studies, at least the ones that Dr. Moorman moderately weighted, don't even measure NDMA at all. The ones that do, for the reasons that Ms. Canaan got into in detail, do not reliably link those levels with an increased risk of the five cancers.

But even if they did, the method Dr. Moorman used to correlate NDMA levels in the dietary studies with real world Ranitidine levels is speculative and unreliable. Nobody else in the entire medical, scientific, and regulatory community has tried to do that and used the dietary and occupational data as a surrogate for Ranitidine use like what Dr. Moorman has done in her report.

Next slide, please.

So, first, let's talk about followup time and whether Dr. Moorman's basis for relying on the dietary and occupational studies is even valid. In other words, what gap do these studies really fill? This is a visual representation of the mean or median followup period in the Ranitidine studies as compared to the dietary studies Dr. Moorman gives the most weight.

Dr. Moorman's claim that followup in the dietary studies is appreciably longer is simply incorrect. The followup periods for these two different bodies of evidence are quite comparable. Even the dietary study with the longest followup, Keszei, has a followup period that is nearly

identical to the mean or median followup period in two Ranitidine studies, Norgaard and Adami in particular.

Our main point is that the evidence doesn't support a claim that dietary and occupational studies are needed to fill any gap in the Ranitidine studies, and again, nobody in the peer reviewed literature has made a similar claim or attempted to use these studies in the manner Dr. Moorman is using them here.

The epidemiology that is available for Ranitidine at this point is extensive, as both Mr. Cheffo and Ms. Canaan got into, and there is simply no suggestion in this large body of evidence that cancer risks suddenly may appear out of nowhere more than a decade after a patient stops taking a medication. There is just no suggestion of that in the data that we have.

Next slide, please.

So, let's talk further about the dietary studies the most fundamental problem I would highlight is that the vast majority of dietary studies relied on by Dr. Moorman, not Mr. Nigh or the Plaintiffs' attorneys, Dr. Moorman, are not NDMA dietary studies at all, meaning they did not measure NDMA at all.

Rather, they were evaluating the potential cancer risks associated with the various foods we have been talking about, with whatever potentially bad substances are in them. The point is that even if one accepts that some amount of eggs

or meat or fish could cause cancer, one could not reliably determine from these studies an amount of NDMA that caused the five cancers. As I said, the vast majority did not evaluate NDMA.

Next slide, please.

You can see that here in this next slide. Of the 39 studies Dr. Moorman gives any weight, 39 do not attempt to quantify the amount of NDMA in the foods being studied. For almost all these studies assessing the cancer risk associated with NDMA exposure was not part of the study.

Because your Honor asked about the Ronco study, we should add that we did not include Ronco in the seven at the bottom here because specific NDMA levels or ranges are not included in that paper.

Next slide, please.

Now, let's look more closely at the seven dietary studies that had information about NDMA levels.

First, out of the seven, Dr. Moorman herself notes that the NDMA estimates in two of them, Zheng -- 2021 NDMA estimates are anonymous and likely erroneous. She gives little or no weight to Rogers, Loh, and De Stefani, three more, based on their extensive limitations.

She gives moderate weight to two studies, this Jakszyn study and Keszei study. I think your Honor asked about both of those. She relies on bladder cancer data from Jakszyn

and esophageal cancer data from Keszei, though Keszei also showed no difference for gastric cancer, and Dr. Moorman left that part out of her analysis.

So, in the interest of time, I am not going to be able to do a deep dive into these two dietary studies that are left, but just as an example, you can see on the right what the authors in Jakszyn concluded, our are findings do not support the hypothesis that red meat and meat related compounds, including NDMA, are associated with the risk of developing bladder cancer. Again, Dr. Moorman is stretching beyond what the authors are willing to do on their own.

Next slide, please.

Now I want to talk about the unique methodology that Dr. Moorman used to try to correlate the dietary and occupational studies to the alleged NDMA levels in Ranitidine that patients took over time.

Dr. Moorman claims the dietary studies are informative because the levels of dietary NDMA in those studies are comparable to the levels in tested lots of Ranitidine. As we have just seen, the NDMA levels in the vast majority of dietary studies aren't actually measured, and the remaining studies do not reliably correlate specific NDMA levels with the cancers at issue here.

Now, with respect to the Ranitidine part of Dr. Moorman's analysis, Dr. Moorman does not specify the total

amounts or amounts per day of NDMA that she assumed patients were ingesting from Ranitidine at a time. She said she relies on NDMA levels reported in FDA's press release, and that might be why your Honor was asking questions about the press releases, but as you will note, that press release contains only the highest and lowest NDMA test results ranging from zero to 860 nanograms.

We have no information on what number in that range Dr. Moorman is relying on as a basis to equate the NDMA levels patients were exposed to over time from Ranitidine to the NDMA levels reported in the dietary studies.

Next slide, please.

It is important to note that Dr. Moorman did not analyze any actual test results. We asked her about that. To illustrate the problem with that we created a graph that contains the FDA's testing of Sanofi's Ranitidine product.

As you can see, FDA actually tested 19 lots of Sanofi's Ranitidine. The overwhelming majority of results, 16 of 19, were below the FDA's acceptable limit for NDMA. They were below the lowest NDMA amounts in many of Dr. Moorman's weighted dietary studies.

I think this tells you why Dr. Moorman didn't at least try to determine a mean or median value within that range. That number would not correlate well with the numbers Plaintiffs are relying on in the dietary studies.

From this graph you could see how hard it would be to try to come up with any reliable estimates of what patients actually ingested in the real world. Dr. Moorman did not provide a reliable methodology to do that, and we are just talking about the levels for 2019.

Next slide, please.

Dr. Moorman's assumptions about the levels of NDMA in Ranitidine before 2019 are even more problematic and speculative.

While the FDA reported a range of test results in 2019, it also said that it has no scientific evidence regarding the level before 2019. Dr. Moorman ignored this part of FDA's statement. Instead, Dr. Moorman tried to extrapolate back and do what the FDA itself said it couldn't do. She just assumed the same zero to 860 or 890 nanogram range for all other years.

There is simply no reliable way for Dr. Moorman to determine how much, if any, NDMA was in any given Ranitidine pills on average or otherwise over any given period of time. Nobody else has tried to do that, not even the FDA, and litigation is not a place to test new methodologies like this for the first time.

Mr. Petrosinelli and Ms. Canaan discussed some of the law that would support that statement.

Next slide. Next slide.

My colleague is moving me along here, your Honor.

*THE COURT:* You have 14 minutes left.

*MR. BROWN:* Okay. I am going to talk about the Bradford-Hill analysis quickly, particularly strength of association, dose response, and replication inconsistency.

I think, because both Ms. Canaan and I are likely going over, we were going to ask if we could take some of our rebuttal time -- a little longer here and take some of our rebuttal time down.

*THE COURT:* Sure.

*MR. BROWN:* Thank you.

First, strength of association, your Honor, there really is no dispute about how important this is in the context of observational studies that produce very low risk estimates and significant confounding challenges. Bradford-Hill puts it first on his list for a reason.

Next slide, please. I lost track here.

Just talking about strength of association and referencing Bradford-Hill puts this first on his list for a reason.

Let's go to the next slide.

He does that because in the observational study world it is notoriously difficult to attribute very small risk ratios below 2.0, let alone below 1.5 to a drug effect. I remember your Honor asking a question about this even at Science Day a number of months ago.

You need such strong evidence beyond a risk estimate above 1.0, and -- or below 2 -- 1.5, I should say, in order to conclude that any small observed difference is due to the medication in question and not population differences that existed from the start, or even the play of chance.

Dr. Moorman acknowledges that here in the slide, conceding that a confounder doesn't need to be very strong to explain weaker risk estimates that are below 2.0.

Next slide, please.

Here you can see that Dr. Moorman did not even try to perform a valid analysis of the relative risks for each cancer. You need relative risks in order to analyze the strength of association and Dr. Moorman says it would be impossible to provide one for any of the five cancers.

Here, Dr. Moorman provides no specific risk estimates that allegedly reflect the strength of association for each cancer.

She knows how important it is to do that because in her report she repeatedly refers to other analogous examples of cause and effect relationships and always includes risk estimates, MP values and confidence roles. She didn't do that here and we believe her failure to do that here invalidates her entire Bradford-Hill analysis from the start.

Let's go to the next slide. And the next slide.

I want to talk about dose response for a minute, your

Honor.

Here, seven different research groups evaluated their data for the presence of a dose response, and with the exception of the nonuser part of Dr. Cardwell's analysis, Dr. Moorman simply didn't like what they found. So instead, as you can see on the left of this slide, she claimed that the studies were so inadequate that you can't really describe anything about dose response, including studies she strongly weighted.

Instead of properly analyzing does response, she also claimed that a single Ranitidine pill can cause each of these five cancers.

Doctor -- oh, Dr. Petrosinelli mentioned this earlier this morning.

*MR. PETROSINELLI:* Thank you.

*MR. BROWN:* This is not a valid analysis of dose response. It's the Plaintiffs' burden of proof to put forward reliable expert evidence to support the Bradford-Hill criteria, including dose response, and dose response is one of the most important factors in this circuit.

I'm going to rap it up and talk about the last factor, your Honor.

Next slide. Next slide. Next slide.

Replication and consistency. In the interest of time, I am not going to read these sections of Dr. Moorman's report, but as you will see, I think it is fair to say that Dr. Moorman

recognizes the importance of both replication and consistency.

Next slide.

Of particular importance here, Dr. Moorman also recognizes how important it is to replicate findings outside a single database or country that a particular study was drawn from. Epidemiologists like Dr. Moorman typically insist on replication because they need to confirm the findings based on a single database aren't simply an artifact of the database or unique to the population being studied.

In her deposition, Dr. Moorman confirmed more than once how important it is to replicate findings in different countries and populations. In the interest of time, again, I won't read the testimony, but you can find it on pages 136 and 137 of her deposition.

Next slide, please.

Now, while Dr. Moorman recognized the importance of replication, she abandoned this important Bradford-Hill factor in relation to her analysis of the Ranitidine studies. Indeed, every study that Dr. Moorman strongly weighted in this case came from a single database in Scotland with a population just under 5.5 million.

The Plaintiffs spent a lot of time in their briefs talking about how the Ranitidine studies that Defense experts rely on do not apply to their U.S. Plaintiffs, but neither Dr. Moorman nor the Plaintiffs explain how they can extrapolate

findings from a single database in Scotland to all of their U.S. Plaintiffs.

Last couple of slides.

By contrast, as you can see here in this slide, Dr. Moorman gave little weight to all the rest of the Ranitidine studies, 11 in all, which examined populations around the world, including studies in the United States where this litigation was brought.

Next slide.

Here, again, your Honor, I won't read the quote, but rest assured that Dr. Cardwell himself acknowledged that his findings in the Scottish database needed to be replicated in other settings, meaning other populations, and that is exactly how Dr. Moorman interpreted it.

Last slide.

This will be it, your Honor. If we zoom out of the Scottish database and evaluate the consistency of findings across the studies Dr. Moorman did not weight heavily, there is very consistent evidence of no increased risk, and that gets to the heart of the Daubert problem in this case.

What you see here is what I just said. On the right a consistent pattern of no increased risk when comparing Ranitidine users to users of other H2RAs. In Dr. Moorman's own words, this is exactly what one would expect to see if there is no association between an exposure and an outcome that has risk

estimates clustered around 1, with some estimates greater than 1, and some less than 1.

In contrast, on the left next to the orange dots, you see selective nonuser analyses that Dr. Moorman heavily weighted and that show some numerical or statistical differences between nonusers and Ranitidine users.

In summary, your Honor, Dr. Moorman used a flawed weighting methodology as a basis to elevate certain nonuser studies from a single database in Scotland and then she used an equally flawed process to invalidate all the active comparator studies which showed no consistent evidence of an increased risk for any of the five cancers. This is not a reliable methodology, and it is why her testimony should be excluded.

Thank you.

*THE COURT:* Okay, thank you.

There is about five minutes left in this main portion, and then you had reserved 20 for your rebuttal.

*MR. HOLIAN:* Your Honor, I had planned on talking 20 minutes. I can keep that to 15. Would your Honor like me to go now or do you want to take a break?

*THE COURT:* We are going to take a break, but we were going to take a break after this presentation.

*MR. HOLIAN:* I want to be sure the Court would prefer I do 15 minutes now, but if your Honor would prefer to take the break and then have me go right after the break --

*THE COURT:* Okay. Now you are going to speak about the experts Le, Salmon, and Michaels. Do you want me to tell you when 15 minutes is up?

*MR. HOLIAN:* Unlike some of my colleagues, your Honor, I have a timer in front of me.

*THE COURT:* You may proceed.

*MR. HOLIAN:* Thank you, your Honor. My name is Matt Holian, I represent Sanofi, I'm here on behalf of all the Defendants today. I will be talking about Drs. Salmon, Le, and Michaels.

A couple of points to put these three experts in context. Unlike Drs. McTiernan and Moorman, they are not epidemiologists, but their epidemiology opinions suffer from some of the same defects as those you heard about from Mr. Brown and Ms. Canaan earlier today with regard to the other experts, which I have shown on this slide, but won't read in the interest of time. There are additional reasons these experts should be precluded as well.

Let's go to the next slide.

I will start with Dr. Salmon. He also offered epidemiology opinions, but should be precluded from offering those because he offered opinions on statistical significance that were inconsistent with what he said outside of litigation, and offered unreliable dose response opinions with regard to NDMA and Ranitidine.

Outside of litigation, Dr. Salmon has recognized the importance of statistical significance. In a book chapter he wrote, shown here on the left, he favorably cited hierarchy classification scheme and noted that a conclusion of sufficient evidence of a causal relationship depends on statistically significant results.

Your Honor, this isn't a book chapter he wrote 40 years ago and never updated, he pulled extensively from that book chapter in the report he submitted here, but when it came time for the section that appears on the left, he omitted that quotation, and instead wrote that statistical significance is not a threshold that must be reached, and he drew a causation opinion based on a pattern of results that he admitted a considerable portion of which were not statistically significant.

Now, turning to Dr. Salmon's dose response analysis, I want to start by showing you the end product of his work. First, in a chart on the left of the slide you will see he calculated NDMA dose response slopes from the dietary and occupational epidemiology studies. Don't worry, the actual specific numbers on the chart you won't have to read. I just wanted to show you the key charts in his report.

He then converted those NDMA dose response slopes into the chart on the right, where he calculated an incremental risk for Ranitidine.

As I will show you, in deriving his NDMA dose response opinions Dr. Salmon used an unreliable methodology. He stacked the deck in the studies that he chose, cherry picked data within studies, and he used an unprecedented method to combine results across studies.

With regard to the first step, Dr. Salmon's report summarizes 28 NDMA epidemiology studies. Of those, he calculated cumulative lifetime NDMA exposure for 20 studies, those shown in black, the others are shaded in gray.

Of those 20, he included 11 in his dose response analysis, and omitted the other nine. And how did he pick which ones to include?

Well, as your Honor can see here, he did his dose response calculations using only the studies on the left, those that showed a statistically significant dose response. He left out the studies on the right because they did not show a dose response.

You can see here in red Dr. Salmon's own assessment of those studies, it is the definition of an unreliable methodology that could only yield one result. It's not that he couldn't do the math, your Honor, for the studies on the right that weren't significant, he could have. It's that if he had done the math, it could show there wasn't a dose response for NDMA, or it at least could have materially affected his results. His explanation, that the studies were uninformative.

Now, it gets worse. Dr. Salmon didn't just cherry pick across studies, he also cherry picked within studies in the Keszei study, for example, you will see here on the right the authors reported eight different results, four different types of cancer for men and for women.

When Dr. Salmon chose to do his dose response analysis he didn't look at all eight, he looked at two, one that was statistically significant, a sub type of esophageal cancer in men, and one that wasn't significant, but that he said was close, a sub type of gastric cancer, again, only in men.

His explanations? Well, he said the data for the six that he left out -- he said the data for the six he left out are a classic example of what data would look like when IARC would say an association cannot be determined. In other words, he left out the data that would undermine his dose response calculations.

And he defended his cherry picking of the statistically significant results by saying, well, I can only reasonably rely on statistically significant results because that is, quote, "the usual standard of scientific reliability."

Of course, if that is true, your Honor, Plaintiffs' entire general causation case falls apart. Again, a quintessential example of a results driven methodology.

It gets worse again. He didn't just stop there. What

did he do with those 11 studies that he cherry picked? He did not follow the procedures for a meta analysis, which, as your Honor may know, is where scientists weight studies based on the number of events, and the Plaintiffs tried to defend what Dr. Salmon did in their briefs by reference to that method, but the Court should not be deceived.

Dr. Salmon did not perform a meta analysis, he didn't weight the studies in any way, he just averaged them. What that means is a study with a thousand cancers gets weighted equally as a study with ten cancers. Nobody in the world thinks that is a reliable way to combine study results.

Not surprisingly, when asked at his deposition, can you point us to anybody who has ever done that, he admitted he could not. No one had ever used this unprecedented methodology.

So, when you stack the deck by cherry picking studies, when you cherry pick data within studies, and then you use an unprecedented method to combine those studies, that makes your conclusions a house of cards.

It gets worse a third time, your Honor. Dr. Salmon didn't just calculate the NDMA dose response slopes and leave it at that; he then applied those calculations to try to derive the risk for patients who took Ranitidine. So, he is stacking the deck with his studies, he is cherry picking within studies, he is coming up with a single average estimate of risk, and

then using that to calculate hazard ratios for patients who take Ranitidine.

That analysis is based on multiple analytical leaps. He assumes every dose of Ranitidine contains a thousand nanograms of NDMA. He assumes the average Ranitidine user takes it for at least ten years based on unspecified prescription records, although he admitted at his deposition he didn't review any prescription records, and said this was a hypothetical illustration.

He solely based his calculations for bladder, pancreas, and liver cancers on the Hidajat study, which you have heard us discuss, and he abandons statistical significance. He doesn't present any P values or confidence intervals for any of these hazard ratios, so there is no way to assess their reliability and there is no way to assess the error rate.

Your Honor mentioned having reviewed 40 scientific studies preparing for this hearing. I'll bet you not a single one presented hazard ratios without confidence intervals or P values. That is just not done.

Perhaps recognizing all of these tenuous assumptions, at his deposition he retreated from this model and labeled it a, quote, "purely hypothetical example." It's question upon question upon question upon question, all built on a house of cards. It is exactly the kind of unreliable speculation and

junk science that Rule 702 forbids.

So, that was Dr. Salmon's quantitative dose response analysis.

At his deposition, Plaintiffs' counsel tried to resurrect his dose response opinion by distinguishing that from what they called his categorical dose response analysis, which is basically just looking at individual studies, so let's look at that.

We have talked a lot about the importance of dose, both dose response and the separate idea of a threshold dose, so I have quoted here some language from the McClain decision.

I wanted to show you what a dose response graph would look like if there was consistent evidence of a dose response. Your Honor, this graph measures two different ways to measure the use of Ranitidine on the horizontal axis, the number of prescriptions on the bottom, daily dose on the top, and has the risk ratio on the vertical axis.

This is what it would look like in a single study if there was a dose response, with the lines sloping upward, the risk ratio going up, as the use of the medication at issue increased.

Scientists, your Honor, don't just eyeball that, they run specific statistical tests to ensure that what they are seeing are not chance findings.

This is what it would look like if there were

consistent evidence of a dose response, multiple studies all sloping upward, and many of them statistically significant. That is what the picture should look like if there is a dose response.

This is what the graph looks like if you show the Ranitidine dose response data. I show here the active comparator results, but the nonuse results are very similar.

As you will see -- there we go -- there is no clear dose response, most of the lines go down. None of the dose response results were statistically significant.

There is one more, the Cardwell study, and those dose response results were only significant when they compared Ranitidine users to nonusers, and only at the very highest dose. Dr. Salmon relies heavily on that result, even though the Cardwell authors specifically noted that there was little evidence of a difference when you compare Ranitidine users to users of other H2 blockers.

When you look at that Cardwell line, your Honor, what you see again is Dr. Salmon emphasizing the data that supports his opinion and downplaying the rest.

Now, you heard Mr. Nigh talk about the defined daily dose measure, but as you will see in the Iwagami study, the red dotted line also used that measure of defined daily dose, and if Ranitidine consistently increased the rate of cancer, the more prescriptions people filled, these lines wouldn't look

this way, your Honor.

Notwithstanding this data, Dr. Salmon comes to the conclusion that there is a dose response for Ranitidine, not just for bladder cancer, but for all five cancers.

Where does that leave him in relation to the rest of the medical community? On an island.

Dr. Salmon said the data present clear evidence of a dose response. He says that for every type of cancer, although he said it is only supportive for pancreas and liver, but that is contrary to what you already heard from Plaintiffs' epidemiologists who say that Ranitidine dose response data were not informative, and it is contrary to what the study authors include. Because Dr. Salmon's dose response analysis is unreliable, his Bradford-Hill analysis is unreliable and he should not be allowed to offer a general causation opinion to a jury.

I will close, your Honor -- we will rest on the papers or discuss in rebuttal Drs. Le and Michaels, but I made a commitment to Ms. Stipes to keep this to 15 minutes, so I will end on this slide.

This is the chart that Mr. Nigh started with, he said, but the Defendants haven't talked about this chart that shows the duration of these studies.

In fact, Dr. Salmon's duration analysis is built on his earlier work and it continues his pattern of cherry

picking. This chart, your Honor, is on page 223 of his 223 page report. If you look at page 221, that is where you see the inputs, the assumptions Dr. Salmon makes to come to these figures.

What you will see is, for each of the five types of cancer he picks one NDMA epidemiology study to calculate the hazard ratios for liver, bladder, and pancreas cancer, solely the Hidajat study, which you have heard us talk about extensively.

For esophageal cancer he uses the Keszei study, but again, he only picks one sub type of esophageal cancer, and only in men.

He also cherry picks the product testing data that he uses to calculate this chart. The FDA max number there, your Honor, the NDMA milligram per year of .31, that is based on pulling the absolute maximum result from all of the tests that FDA did from all of the manufacturers, and he assumes that every person who took Ranitidine gets exposed to that level for the whole time they take it.

Even when you make those assumptions, Judge, you will see -- Dr. Petrosinelli stole my thunder -- that for bladder, pancreas, and liver cancer you have to take that extreme level, you have to be exposed at that extreme level for at least 27 years. You can see it slightly shorter for gastric and esophagus.

That doesn't get the Plaintiffs there so they have to overlay on top of that all of Dr. Najafi's testing to try to shorten those durations.

Your Honor, I will close by saying, you will hear more about that tomorrow, that is not a reliable way to answer the call in McClain to say how much is too much, and the Plaintiffs can't have it both ways. They can't say the Ranitidine epidemiology is too short. It doesn't answer the question if the durations in Dr. Salmon's analysis hold true, because if they did and if Dr. Najafi's test results were actually experienced by patients taking Ranitidine, you should see it in the Ranitidine epidemiology.

Thank you, your Honor.

*THE COURT:* Thank you. That was 15 minutes.

That leaves you with ten minutes for your rebuttal. Is that what -- you agree?

*MR. HOLIAN:* Yes.

*THE COURT:* It is 2:55. We will be in a 15-minute break, so we will come back at 3:10 and then we will hear from the Plaintiffs.

So we will be in recess.

(Thereupon, a short recess was taken.)

*THE COURT:* You may be seated. Thank you.

Okay. Now we can hear from Plaintiff's counsel. Is it Mr. Ronca who is going first as to Dr. McTiernan?

Do I need to give you any kind of a warning or do you have the time covered?

*MR. RONCA:* I have the timer.

*THE COURT:* Okay. Good afternoon.

*MR. RONCA:* I have not appeared before you before, your Honor, I am Tracy Finken's partner. I am here today to argue in opposition to Defendants' motion to exclude the testimony of Ann McTiernan. We urge the Court to deny the motion.

Ann McTiernan is a full professor of epidemiology at the Fred Hutchison Cancer Center affiliated with the University of Washington, where she was previously director for a decade.

Most of her over 400 peer reviewed studies relate to cancer. She has extensive experience in both diet and cancer risk with over 130 studies, and cancer risk of medications and supplements with over 70 studies, including cancer risk of aspirin, Tamoxifen, and Vitamin D, in other words, pills you are taking and which may or may not increase the risk of cancer.

Dr. McTiernan is the only epidemiologist in this litigation who has served on both an IARC working group and at WCRF on an expert advisory panel.

Next slide, please.

She has done studies, peer review, and grant review for the most important cancer institutions and agencies in this

country, including the National Cancer Institute and the Women's Health Initiative, and many international institutions also.

She has been involved in one other litigation, the Talc litigation, where she passed all of her review, and frankly, the Defendants don't seriously challenge her qualification to testify in this case.

As the other speakers have done, I will give you a little bit of a road map. I don't have a road map slide, but I will let you know when I am changing topics, because it might be clear in my head, but might not be so easy for the listener.

First I am going to talk about the accepted scientific method Dr. McTiernan employed in reaching her opinions. After that, I am going to talk about the research question in this case. Third, dose response. Fourth, dose, including the legal question regarding dose. Fifth, a discussion of the active comparator studies that we have heard so much about today.

Sixth, I want to give a detailed example of how Dr. McTiernan delved into the studies to find their true strengths, weaknesses, and weight, which defeats the Defendants' arguments of cherry picking and a predetermined result.

So, I think that will be instructive because we'll dive in, maybe not like we are supposed to as lawyers and judges, but looking at it the way a scientist looks at it.

Seventh, we are going to talk about the

inconsistencies of the studies in finding an increased risk of the five cancers, and as I will show later -- we have heard a lot about there being no association, you need an association before you get to the Bradford-Hill criteria. I am going to show a lot of associations.

Then, if I have time, I want to rebut some of the specific Defense allegations related to the World Cancer Research Fund, the reference to Dr. McTiernan's testimony in the Talc litigation, and if I have time, some of the partial statements made by the Defense in their papers.

Let's go to the next slide.

The scientific method employed by Dr. McTiernan is a weight of the totality of the evidence and then the application of the Bradford-Hill criteria for causal inference. The method is well accepted in both science and law.

As was made clear in the Abilify case, the weight of the evidence approach can be considered reliable provided the expert considers all the available evidence carefully and explains how the relative weight of the various pieces of the evidence led to her conclusion.

This method requires the expert to exercise judgment, which requires the expert to describe each step in the process by which she gathered and assessed the relevant scientific evidence. Dr. McTiernan met that burden by accumulating and reviewing the totality of the evidence in exhaustive detail.

Sometimes we lawyers like to see bright lines, like the fact I did a road map, one, two, three, four, five, six, this is what you have to prove. In science, and actually in law, judgment sometimes, and often frequently, is the result of the research.

So, in science, judgments are made all the time and based on science, governments, institutions, medical facilities, physicians, make decisions all the time based on scientific judgment. So, there is nothing wrong with a judgment being made once the evidence is carefully reviewed.

It doesn't have to meet some abstract criteria. It is a judgment, and if it is done properly, it is admissible.

Now, the first item is a systematic search and accumulation of all the scientific studies and literature for review. The Defendants do not even challenge the completeness of Dr. McTiernan's search and gathering of the evidence. Totality of the evidence is not an issue.

Next slide.

In the Abilify case Judge Rodgers detailed five factors to be shown when using the weight of the evidence method, and I want to align that with that list of things that Dr. McTiernan did, which I took out of her report.

First is whether an association is shown.

This comes from the data in the study, not only the results, but all the factors that lead to those results. The

review Dr. McTiernan employed was applied study by study, including the study type and design, most case control and -- mostly they were case control and cohort studies, and the design is important. Okay.

If you look at the particulars of the design and make an expert judgment on whether the design can even give you the answer that the study is supposed to give.

Second, the population source and specifics of the population. For example, how young or old is the population. You will have a hard time finding a lot of cancers in a very young population, or as I heard in a lecture once, you won't find a lot of post menopausal symptoms if you only do a study of college women.

Depending on the population you are looking at, in this case in particular there was one study where more than half of the participants were below age 40, meaning you are not going to find many cancers in that more than half.

Another study only looked at patients who were men and who had H. pylori. Now, if you are trying to find out whether exposure to Ranitidine can increase the risk of cancer for people with H. pylori, that would be a good study. Is it generalizable to everyone? Probably not, but that is what the expert needs to look at specifically study by study.

The expert needs to look at the risk ratios, including relative risk, statistical testing. Yes, there is a debate

about statistical testing. Yes, it should be done in every case. No, it is not the sine qua non of this is the answer. If it is statistically significant you count it, and if it is not statistically significant you don't count it.

That is not so. Statistical significance only measures the chance in that data set, not the chance overall. If the data set is poor, then it doesn't matter if it is statistically significant. Again, things that experts need to review when doing a systematic review.

Dose, including the amount and duration, dose response and the outcome definition and measurement, in other words, how was the outcome determined. Was it pathology reports? Was it medical records? Was it insurance codes? This is why the FDA has concerns about electronic databases being used because, why was that code being used? That code is being used to pay a bill, not -- and those kind of electronic databases are not research databases.

There are large research databases. The dietary studies that are used in this case, one of them uses, for example, EPIC, which is a giant research database created in ten countries in Europe to study diet, set up by researchers, not insurance codes.

You can see from Dr. McTiernan's report that she considered each of these in detail study by study.

Now, the second item is alternative explanation for

the association, and this includes issues of confounding and bias, and other sources -- in other words, did we get the result because of some problem with the study itself?

I am not going to delve into all those various definitions of bias and confounders because there are many. I know the Court has exhaustively read all the reports and seen it over and over again. But they are important to review, and when we get to that example I mentioned that we were going to talk about, you will see an example of where that comes in.

Some of the bias, like watering down a study population, can also reduce the amount of risk. On the other hand, if you overstate certain outcomes because of the study population, you can get a higher risk where it really shouldn't be there.

Experts need to review that and make judgment calls on what the value of a study is based on that and, as Judge Rodgers put it, there are alternative explanations for the association.

Next, rank reliable explanations, in other words, weighing the studies. I am going to rank them, I am going to weigh them based on all those other things that I reviewed, study by study, and finally consider all the relevant now available evidence, and so that is all the relevant and available evidence.

The Defendants in this case very clearly want to limit

the review to Ranitidine specific studies, even though the contaminant is NDMA. They don't want us to look at the NDMA studies, but the NDMA studies are relevant. They may not be the most important evidence, but the NDMA studies are relevant to the question that we are raising here.

Second, compare consistency between studies. I will show that to you later, I hope. Compare to results of animal studies, compare to the results of in vitro studies.

For example, if the substance doesn't cause cancer in any animals or none of the in vitro studies come up with a genotoxic or a carcinogenic, but you see an increased risk in human studies, there is a question. Well, is it this toxic agent or is it something else?

When they are consistent, when the animal studies show cancer, when the in vitro studies show carcinogenicity, when the human studies show an increased risk of cancer, that is a consistency that can support an opinion.

Case reports, like FDA adverse event reports, there is the McGwin study, it should be considered. It was considered in this case, but Dr. McTiernan didn't give it any weight, just gave it weight as a signal.

Then the last thing the expert has to do is integrate the evidence using professional judgment. This is where you apply what is commonly called the Bradford-Hill criteria, or viewpoints or factors. None are required, one would be

sufficient if it were strong enough, but the important thing is for the expert to take all the information that we just talked about and condense it, look at it within the concept of those viewpoints and then come to a scientific judgment about whether a connection can be made between a particular toxic agent and cancer.

In this case, Dr. McTiernan first did a lengthy discussion of all of the studies and the databases that supported those databases, where did that data come from, and then she went through a detailed examination of each cancer separately, and then applied he Bradford-Hill criteria.

She did three things, and I am going to point this out now. I don't have time to give you specific examples.

Many times -- in those representations that the Defendants made here today, they took a piece from the general discussion and a piece from the Bradford-Hill discussion and tried to say that those two things were the same thing, but in the first piece, that is when Dr. McTiernan is going through all the specifics of the studies, and the second piece is where judgments are being made.

There is a fair amount in the Defendants' papers of taking parts of sentences without what went before and what went after, two or three words in quotes, and calling that what Dr. McTiernan said, or taking one quote out of a 13-hour deposition. Okay. That is fine as long as everyone who is

making a decision relating to this keeps in mind that there is a longer answer there, or the answer might have been at the next question, and when you pull out a snippet, it doesn't necessarily reflect everything that happened in the 13 hours.

Go to slide 5.

So, the Defendants don't even dispute that this is the right method. In fact Dr. Terry, who is one of the Defendants' epidemiology experts, basically gives the same description in her report on pages 20 and 21.

Go to 6, please.

It just follows on from what I just said.

So, the important note in this is that Dr. Terry agrees that there are no perfect studies, and because there are no perfect studies, let alone perfect observational studies, it is important for an expert with the type of qualifications that Dr. McTiernan, or for that matter Dr. Terry has, to review.

Two experts reviewing the same data could come to different scientific judgments, but that doesn't mean that either judgment is either more persuasive or better. It just means that they have a disagreement, and those disagreements, as I understand the case law, are decided by juries.

So, Dr. McTiernan followed scientific method, when a study had a good solid foundation, she put extra weight on it. When a study was riddled with problems, like short exposure or short followup periods, lack of dose information, and on and on

and on, then she called it, and she put less weight on that study.

Throughout her report she explained in detail, exhausting detail, exactly what she was doing, and the bottom line of the argument so far is that the Defendants do not challenge Dr. McTiernan's qualifications. How could you? Defendants do not challenge the breadth and depth of the evidence that Dr. McTiernan accumulated, and they do not challenge the method, the design of the method that she used.

What the Defendants challenge is the way Dr. McTiernan evaluated the studies. Defendants want the Court to decide which studies should be considered and which are the better studies.

As stated by Judge Chhabria in the Roundup, the Daubert inquiry does not require or even allow a District Court to exclude an expert's opinion merely because the Court is not persuaded that the expert's read of the evidence is the best one, or make conclusions on the persuasiveness of the proper evidence.

The test is not the correctness of the expert's conclusions, but the soundness of her methodology, and applying the Bradford-Hill criteria involves a certain amount of subjectivity, and experts disagree when doing that. This is not my word, these are the words from the Roundup case. The Court's job is to make sure that the expert's methods are not

so far outside the realm of reasonable scientific practice that the testimony would be unhelpful to the jury. So far outside the realm of scientific practice, that is not what we have here.

Now, next slide, please.

So, Dr. McTiernan's charge was to look at all cancer and exposure to Ranitidine, and in particular the lawyers, us, told her to look specifically at ten designated cancers, and she did.

She went through each one with the depth and rigor that I just described, and then she turned back and she said to the Plaintiffs, in my opinion, for five of these cancers there is sufficient evidence to show an increased risk of harm -- increased risk of cancer when exposed to Ranitidine, and we are talking about chronic exposure, long-term exposure, not very, very short exposure.

But she also said, on the five other cancers, in my opinion, there is not enough evidence for me to say that. I am telling all the Plaintiffs who filed lawsuits based on the other five cancers I cannot help them. It doesn't matter that more cancers than that got past Daubert in the Valsartan case, and it doesn't matter that other cancers, other than the five, got past in a State case recently. That didn't matter to Dr. McTiernan because Dr. McTiernan is not cherry picking her results.

If she were cherry picking her results, if she had a predetermined result, then she would have gone with ten cancers, or eight cancers, or seven cancers. She wouldn't have eliminated five cancers or cancers that have gotten by in other Courts.

I mean, she probably wanted to help us, but told us she couldn't, and this is the best evidence, I think, that there was no cherry picking.

And just as an aside, my very able opponent, Mr. Cheffo, pointed out this morning that both Dr. McTiernan and Dr. Moorman did not use the same data -- did not use data to favor the Plaintiffs with respect to those cancers.

So, this is what happens when you try to go from something that was said earlier and put it into your prepared remarks. I apologize for slipping up a little bit.

Next issue, we are going to go to the research question. What is the research question? If you look at the papers you are going to see it two ways, NDMA in Ranitidine, or Ranitidine containing NDMA. Which is it? This is a distinction without a differences.

Next slide.

The issue in the case is not Ranitidine. The Plaintiffs have not offered an expert report saying the Ranitidine molecule causes cancer. Ranitidine is not off the market because of the Ranitidine molecule, it is off the market

because it turns itself into NDMA. It is a salt and it breaks down, particularly if it is wet, and it becomes a different substance, part of it, depending on how long, more and more of it, and it carries it into the human body.

NDMA is a toxic contaminant and NDMA is the cancer-causing agent. No matter how you phrase that, that is the research question.

And the Defendants want to phrase it Ranitidine containing NDMA because they want you to isolate your focus only on the Ranitidine specific studies.

Now, next slide, please.

Now, I want to talk about dose and dose response at this point. It was brought up before, and part of my argument comes out of something the Defendants say the failure to address dose and the complete absence of dose response is also fatal to the Plaintiffs' expert opinions.

I am not sure how the Defendants can make this statement because Dr. McTiernan covered both of those subjects in spades, I mean in detail, and to say that, for example, complete absence of dose response information, that is jut wrong if you read her report.

Next slide, please.

Let's take a look. Dr. McTiernan specifically discussed dose response in each study. For example, in Adami, on page 127 and 128, dose medication was not assessed in

relation to cancer, therefore dose response was not presented in the paper. She did that for every study. Every dietary study, every Ranitidine study, every occupational study, she looked in the data from the study and said, did the authors address dose response, and then made a comment.

So, to say that she didn't take those responses into account is just wrong.

Let's look at another example, Cardwell. In Cardwell they had a defined daily dose. They knew how much Ranitidine each subject was getting, and for how long, and they were able to define it down into years.

So, what Cardwell showed was if you looked at people with one year of exposure, they had a certain risk, and if you looked at people with three years of exposure, they had a higher risk. Who is that against? Nonusers, which is the background risk.

The bottom line is that Dr. McTiernan talked about dose response and whether or not that information was in the study for each study.

Next slide.

You know, the point, this comes out of a recent Eleventh Circuit case, Williams versus Mosaic Fertilizer, is that a specific amount of dose is not required, particularly when we are talking about general causation. What the Court requires, what the Eleventh Circuit requires is that the expert

lay a reliable groundwork for determining the dose response relationship.

How do you have that groundwork? You start with the foundation, you look at the studies themselves. You see what dose response information they have, and when you get to your totality of the evidence, your systematic review, and you get to your Bradford-Hill, you talk about the biological grading or dose response. If I get more, do I get more cancers? That makes sense, and that is exactly what Dr. McTiernan did here.

The Defendants want to characterizes this as, Doctor, what is the minimum dose a person needs to be exposed to Ranitidine in order to get cancer? That is not the question. It is not the question. It isn't dose.

It is the question of whether a realistic dose can lead to an increased risk of cancer at this stage.

Next slide, please.

So, let's talk about dose. I jumped myself here by not having the slide up, but whether a reasonable jury could conclude that the NDMA in Ranitidine is capable of causing human cancer at the highest realistic dose. Think of, for example, Roundup, which is the landscaper who sprays Roundup all week, every day, 300 days a year, and wears no protection. If that person could potentially get cancer, and there is evidence to support it through this type of a review, then the Court should pass on -- whether an individual got cancer, it

should pass that on to the jury.

Now, I want to get into the concept of dose here, and I think I might be getting ahead of myself, but I will do it now anyway.

So, your Honor, what the reference manual talks about in respect to dose is -- and even dose response, is that at the general causation level, the reason why the question is phrased this way is because you've got a whole set of individual Plaintiffs out there, and at the specific causation level other factors are going to come into play in determining whether that individual got cancer, other factors that don't play in now.

For example, I mentioned before about a person has H. pylori or doesn't have H. pylori. What if the Plaintiff was a smoker, and had diabetes, and was overweight, and got cancer, versus a person who was clean living and younger, and didn't have any genetic propensity toward a cancer, and takes Ranitidine and gets a cancer.

Those types of analyses, which the reference manual calls differential etiology, similar to differential diagnosis, need to be done at the case specific level once you show on general causation that realistic doses, the doses you can get from the drug, could cause cancer.

Next slide.

So, in Dr. McTiernan's evaluation and in her report there are two answers to this question.

There are Ranitidine specific studies with actual doses of Ranitidine taken by actual patients, for example, and the best example is the Cardwell study where they know, define daily dose, how many days, how many milligrams they are getting, and they see an increased risk of cancer, those are realistic doses. Those are doses being taken by real people.

So, a realistic dose in this case, at least for bladder cancer, is answered, but a secondary way of proof is through human NDMA exposure studies through diet and occupation, because if NDMA is the toxin, and you know how much NDMA people are being exposed to, then you can answer the question about whether or not the doses in the pills, where we know some of the testing is on that, is equivalent to the kind of dose of NDMA you get or exposure to NDMA you get from, let's say, beer. Okay.

So -- and again, another aside. Beer manufacturers went to great lengths to get rid of the NDMA in beer some years ago. Why? For the same reasons that Ranitidine is off the market. Okay.

Next slide, please.

Okay. So, I already mentioned McDowell and how specific the dose is in McDowell. Some studies try to use prescriptions as a proxy for dose without knowing whether the amount prescribed was 75 milligrams, 150 milligrams, 350 milligrams, could even be 600 milligrams, and for how long.

Was the prescription for two weeks, 30 days, 60 days, 90 days? If you don't know those things prescriptions can be a poor proxy for exposure.

What if you had -- let's think of the study that looked at ten prescriptions. Are the ten prescriptions one this year, one this year, one this year, one this year, or are they all in a row, or it said greater than ten, how many of those people had 50 prescriptions versus how many only had ten?

Those types of considerations have to go into the determination of what weight you put on the dose information in the studies that you are looking at.

This is the kind of thing that Dr. McTiernan did through and through and through her report.

Let's go to the next slide, please.

Okay. Active comparators. So, the Defendants say that the Plaintiffs' experts disregard the key control against false positives in Ranitidine studies and in pharmaco epidemiology generally, active comparators.

That is not what happened. Dr. McTiernan and Dr. Moorman reviewed each study and how they used active comparators. Adami, for example, had little information on why the various H2RAs and PPIs were prescribed. So, there is no way to know if the drugs were given for similar disease conditions.

This is important, and Dr. McTiernan said this several

times in her deposition and in her report, but the thing you need to look at when you are trying to determine if your study is balanced by using an active comparator is, what is the data in the study.

I am going to show you later when I do those examples, in, for example, the Adami study they didn't have the data on why the drugs were being prescribed, although they could have gotten it. The study should show this percent of them are getting it for GERD, and this percent are for Barrett's esophagus, and this percent for erosive gastritis, and this percent for ulcers, and then you would know if the two groups, the Ranitidine group or the PPI group, or maybe a third group, another H2RA group, you would know that they actually are balanced.

It is not scientifically -- maybe legally they want it to be this way, maybe in argument they want it to be this way, but it is not legally appropriate to make a determination simply because you say this is an active comparator study and that takes care of everything. That is not the way it goes.

In particular, I want to point out the guidance that was referred to several times. That guidance says it is not intended to be prescriptive with regard to the choice of a study design or a type of analysis, and does not endorse any particular type of data, resource, or methodology. It does not provide a framework for determining the appropriate weight of

evidence to be given to studies.

That is the same document that the Defendants are referring to. For active comparator studies to work you have to have the same disease, the same level, the same severity in the exposed cohorts, and there are other factors, too.

What if your formulary pays for Ranitidine and doesn't pay for Cimetidine; you are going to get Ranitidine, not because of your condition, but because of the formulary. That is a factor in that FDA guidance.

Next slide.

Now, this is going to lead into that example I want to give. I am calling this false accusations of cherry picking. That might be a little strong, I wish I could take that word back, but I already typed it up.

The Defendants said that Dr. McTiernan relies on the unadjusted data in Adami, so she picked the unadjusted data or crude data from Adami because it was more favorable, but she relies on the adjusted risk estimates from Norgaard. That is a criticism, that is not what she did.

Next slide.

This is the example I told you about. Three studies from the same database in Denmark, the Potagard study, the Adami study and the Norgaard study, all discussed on pages 121 to 132 of Dr. McTiernan's report.

Dr. McTiernan analyzed all aspects -- next slide --

and first in the Potagard study, that was a screening study, it looked at lots and lots and lots of drugs. There was a high value for stomach cancer that favored the Plaintiffs. What did Dr. McTiernan do with that? She did not include it in her causation. If she were cherry picking, she would try to, but she did not include it at all.

Next slide.

In her addendum report Dr. McTiernan describes when she saw the corrected Adami study that she saw some anomalies in the numbers, so let's look at that.

This is a busy slide, I'm just showing you that I copied these right out of the studies themselves.

So, on the left in blue are the crude, on the right are the adjusted or corrected or adjusted numbers.

What Dr. McTiernan noticed when she looked at that was -- next slide -- for most of them, when you look at the Ranitidine and you compare the crude to the adjusted the cases went down and the person years went up.

For the other H2RAs the cases went up and the person years went down, and the effect of that is you compress all the results toward the null value, toward 1.0. That is what the adjustments did, and as she said in her report, Dr. Adami did not describe in the published paper what the basis for these changes were.

It is called trimming, you are trimming it because

your data sets don't match, so you try to trim to get them to match up better, but it doesn't always come out accurately.

So, for Adami, Dr. McTiernan used the crude, which she reserved the ability to do. All the way in the beginning of her report she said that if I find there are problems in the study, I may use the crude; otherwise she used all adjusted.

And in fact -- next slide -- with respect to Norgaard, from the same university, same data, she used the adjusted risk which is lower than the crude risk. So, a cherry picker would have used the crude risk in Norgaard because it is higher and it is statistically significant, but Dr. McTiernan did not do that because she is not a cherry picker. She used the adjusted risk, which is lower and didn't have that statistical testing significance.

So, when you look inside the studies what you see is -- and I have given at least three examples now where Dr. McTiernan could have gone the other way and did not.

Next slide.

Now, remember I mentioned before about how well are the indications listed in the study, because active comparator, similar indications. Here is the data that Adami had in their study for gastroesophageal reflux, Barrett's esophagus, and gastric or duodenal ulcer, less than seven and a half percent information, and it's probably less than that, because some people probably had two of those things.

You can't assume just because it is an active comparator study this is taken care of, especially in a study that had no information on smoking, had no information on drinking, and several other high risk factors.

Next slide.

Also, there is an issue of the size of the cohort that Dr. McTiernan noticed. In Adami, now same cohort, Ranitidine users from Denmark, Adami went from one prescription and Norgaard went from two prescriptions and when you he went to two prescriptions, that cut out two-thirds of the people.

What does that mean? That means that two-thirds of the people only had one prescription. How many cancers does anybody expect to see from one prescription? None. What does that does is, it dilutes the numbers and brings the odds ratios down.

Next slide. Next one. That was my two-thirds slide.

And the Defendants claim that the Plaintiffs' experts rely on supposedly weak associations.

Next slide.

They quote from the reference manual that anything less than 2.0 is noise. Well, that is not from the reference manual -- it is from the reference manual, but it is from a footnote, and it's one commentator said that.

The reference manual itself says in the text, while this reasoning has a certain logic as far as it goes, there is

a number of significant assumptions and important caveats, and it goes into them. We don't have time to go into them now.

Next slide.

In In Re Roundup the Court said, although the magnitude of the observed association in each individual study was not especially large -- another Bradford-Hill criteria -- consistency allayed his concerns about chance and bias, leading him to ultimately conclude that case control studies demonstrate a significant strength of association.

Next slide.

Similarly in Abilify, talking about association is consistently observed by different researchers using different methods on different populations.

Next slide.

All right. You have seen forest plots today made by lawyers. Dr. McTiernan didn't use any forest plots because they can be misleading. They don't say anything about the strength of the studies, or whether there is confounders, it is just the results. Okay. But they can be useful and Dr. Terry, one of the Defense experts, did use it, and so, this is bladder cancer.

Next slide.

This is not something that we created, this is something the Defense experts created. All right.

Next slide. There we go, okay.

For bladder cancer -- first of all, 16 out of the 20 results are to the right of 1, and five of them are statistically significant. Here is the associations that we are talking about, Judge. They say there is no valid associations.

These are not the results that the Plaintiffs picked, these are the results the Defendants picked, yet it still shows consistency on the right side of 1, and five statistically significant increased risks, and I defy anybody to look at this and not see a pattern, a pattern of increased risks.

There are various reasons why these studies have wider or narrower confidence intervals. Those are the things that Dr. McTiernan discussed in all that detail she was going through, the reasons for that, but you can't walk away from the results. There are five statistically significant results, five associations.

Next slide.

This is Dr. Porter, another Defense expert. This slide represents every single bladder result he reported in his report. I took his deposition, he confirmed it. All of them are to the right of 1.

Next slide.

This is Dr. Vasi, another Defense expert, his forest plot. Very similar to Dr. Terry's forest plot, five results that another Defense expert reported on that are to the right

of 1.

Next slide, please.

Let's not limit it to bladder, let's look at stomach and gastric cancer. This is Dr. Terry's chart.

Next slide.

Now, if we take Dr. Cherry's -- Terry's chart -- I think I reversed it, I said cherry tart -- Dr. Terry's chart, take out the Y Kim study, which is a bad study, a poorly done study, take out those results, what do you see? You see, I think, almost every one is either close to 1 or to the right. There is only one outlier far to the left and that is Dumar, and one of the ones to the right is statistically significant, and I call that an association.

Next slide.

Let's look at liver cancer, okay.

Next slide.

Add the line at 2, since 2.0 seems very important to certain people.

Let's go to the next slide, which will take out Kim.

Okay. So, again, an expert could see a pattern here, an expert could see three of the study results approaching 2. An expert could see a pattern here of one study being statistically significant. Okay.

So, two other things. I have two minutes according to my colleague, and I will try to cover these fast. Okay.

One is this complaint about the World Cancer Research Fund, WCRF, and they don't rely on control studies, and that Dr. McTiernan used a different methodology with respect to that than she did for this report.

Okay. This is explained by Dr. McTiernan in her testimony. WCRF relies mostly on meta analysis. Usually you can't use case control studies in meta analysis, but Dr. McTiernan also said that for certain types of cancers and for certain case control studies they do consider case control studies.

The second thing that was pointed out -- she describes a whole process that really has nothing to do with this case because the purposes of that organization are different than our purposes here.

The bottom line is that they do consider case control studies, and you know, it was pointed out in Ms. Canaan's presentation that NDMA was not considered -- it was considered, I think, limited, no association, limited, no conclusion, limited, no conclusion.

Dr. McTiernan explained that that was based on the 2005 to 2007 data, and Ms. Canaan showed you earlier that there is a table that shows four additional studies that are on their list, but in the 2018 version, two years later, which is also referenced in their briefs and in the PowerPoint you saw today, it literally says that the following exposures were not updated

as part of the 2015, and the last time they did it was 2005 to 2007, and listed right there is NDMA.

Dr. McTiernan was right, it was not updated. If they had all the data they had now, like the Hidajat study, they may well have put it up in a different category.

The Defendants want to say everything is fixed in time, because that was the conclusion in 2005 to 2007, it applies now, without looking underneath in the same document on page 41.

Real quickly on Talc, your Honor, I think this is easy to get. In Talc, for your exposure, you are talking about can I remember if I used talcum powder on my body. Some people use it every day, and they can say I used it every day for five years. That is one type of exposure, and that is easier to remember and has less recall bias.

On the other end are dietary studies where you have like 150 or 200 items on a food frequency questionnaire, and people fill that out and there are worries about the accuracy.

Now, there are plenty of studies validating that method, and huge studies that were relied on in this case, like the Epic study, that rely on that method.

There is a place in between that the Defendants didn't talk about, and that is when you are talking about a specific nutrient like beer, or meat, or certain types of meat, and when you ask people to recall those things, your recall bias is much

less than it would be if it was 150 things and more than if it is one thing.

It is not that simple to look through the lens and say, recall bias wrecks all of Dr. McTiernan's opinions. It does not. You have to look at the individual studies, which is what Dr. McTiernan did. I think I said it ten times now.

So, there is really no question about qualifications, there is no question about the election of the method, no question about the amount of material she reviewed. The only question is, how did she do the studies?

And we believe that she did them in the way they should be done, in a way that is reliable, in a way that meets all the scientific standards, and in a way that a jury could understand, so we ask the Court to let this case go through the gate.

*THE COURT:* Okay. Thank you very much.

*MR. RONCA:* Thank you, your Honor.

*THE COURT:* That was going on 50 minutes. Mr. Heinz is next for Dr. Moorman.

*MR. HEINZ:* Good afternoon, your Honor, may it please the Court.

*THE COURT:* Good afternoon.

*MR. HEINZ:* Could I be permitted to use my cell phone in airplane mode to track my time?

*THE COURT:* Yes, you may.

*MR. HEINZ:* My name is Noah Heinz, I am going to talk about Dr. Moorman. Before I start that, I want to say that I wouldn't be able to argue here today were it not for the Court setting up the Leadership Development Committee and the full support of the co-leads, and I am highly thankful for the opportunity.

I am first going to talk about Dr. Moorman's qualifications and her methodology. After that, I will rebut six lines of argument that I heard from the reply in the briefing, and also from Mr. Brown's presentation about Dr. Moorman, and then last, I am going to apply Daubert case law and try to wrap it up in that way.

I am going to return to the case law at the end, but I think it is helpful to think about it now as I go through the arguments and draw out two points from Abilify.

The first point is that reliable methodology has to have at least one of three primary methodologies, including epidemiology, dose response, and background risk. So, that is the first point.

As you are listening to these arguments, think about did Dr. Moorman have at least one of those three.

The second point is that judges should not evaluate the persuasiveness of the different studies. That is also something to consider, so you have to have one of the primary methodologies, but it is not supposed to be about the

persuasiveness of the individual study.

Qualifications.

Dr. Moorman's qualifications are largely conceded by the Defendants, and for a very good reason. She has a Ph.D. in epidemiology. She is obviously qualified to talk about that. She has published 150 publications on cancer, or many of them are on cancer, not necessarily all of them, and she has been a tenured professor at Duke Medical School where she has taught epidemiology for almost -- more that 20 years. She retired just last year actually.

There is not much question that Dr. Moorman is qualified, and again, Defendants essentially agree.

So, methodology. That is what Daubert is supposed to be about, methodology, and not conclusions.

What did Dr. Moorman do? She looked at all of the evidence, considered everything for Ranitidine, everything for NDMA, and then weighed it and applied Bradford-Hill, so looking at all the evidence.

Defendants agree she looked at all the evidence. They didn't say that she missed anything important. Check on that, undisputed.

What did she do next? She evaluated each of the different studies, whether that is on Ranitidine or on diet or animal studies, any different type of study, and looked using a few different criteria, and there is a lot of focus on just

three criteria, and those are important, talking about dose, followup, the size of the study, that kind of thing.

Dr. Moorman considered more than just that, and I would say, as we said in our brief, you know, it really came down to six or seven factors, it kind of depends on how you count it, but I will say six that she went through.

First was the study type, that was something to consider. Is it a case control study, is it a cohort study, what type of a case control, for example. This really matters because different critiques apply differently to different studies.

I saw some things that were a little bit confusing on some of the slides, things like there is a followup period for case control studies, things like that. Dr. Moorman explains in her report there really isn't such a thing as a followup period for a case control study, for example, so it is really apples and oranges at that point. You can't apply the exact same followup paradigms to case control studies. That is the first thing, the study type.

Second is study size. That is self explanatory. If it is a lot of people that means something.

The third is exposure to Ranitidine or NDMA, and this has -- the first is the most obvious thing, the dose. What is the dose? Was it just anybody who ever took Ranitidine, who ever had any NDMA? That is going to be a little bit less

useful, maybe a little bit useful. Or does it have very detailed information about it? For example, defined daily dose.

That would mean you need not only the number of prescriptions, but also is it 75 milligrams, 150 milligrams, 350 milligrams? How many times did the person take it? There is a lot of information that goes into dose beyond just the prescriptions even if you have that.

The next thing, which is still on exposure, is the accuracy of the exposure information. There is a world of difference between asking people what they did, self reported information, for example, did you take Ranitidine in the last 30 days, compared to pharmacy records, because people don't necessarily know what type of medicine they took. They might think it was Ranitidine, but it was actually Cimetidine. People often make mistakes on surveys. Dr. Moorman pointed that out, for a couple of the studies that the numbers didn't quite work out. So you really care about accurate data that comes from pharmacy records or something like that.

This is really a big concern that you heard from Mr. Nigh with the Kim study, for example, it really fits into this bucket, that it was an aggregated database and it was from insurance claims, and there are a lot of questions with that kind of data. How accurate is it, and what kind of conclusions can you draw from it? And Dr. Moorman certainly considered

that for this criteria.

The fourth one is the followup time, so whether the followup time was adequate to detect cancer from long-term exposure to Ranitidine, and it is fairly obvious why that would be important, and to sort of think about why it might be, I want you to think about the chart that you saw the Defendants put up about cancer and smoking.

They said this is what dose response looks like, and then they had ten years, and it looked to me like about 1.2. It had 20 years, and it went higher, 30 years, it went higher, 40 years, it went higher, 50 years, it went higher.

If you had something like a followup of just one or two years and dose information that was just one or two years, you would be below the very first part on that mark, so it would be less than 1.2. You would barely be able to track anything, so the followup is critically important.

Next is whether the study accounted for over-the-counter use, other things like that, switching from one acid suppressant to another. This criteria is really all about misclassification.

There are a couple of different forms of that. Switching is an obvious one, you were using one medication and then used another one. It is hard to classify where that person should fit, but over-the-counter is another example. You're taking a different drug from the one that is tracking in

the survey, only looking at the prescription records.

The last one would be whether the study accounted for bias, and confounders, obesity, smoking, alcohol use, and other medical conditions, things like that. Again, Defendants agree that Dr. Moorman identified all the right bias and confounding factors. They conceded that and said, yes, she caught all of them. They just disagree with how she applied that. So, this criteria is definitely right.

She applied these criteria consistently. She looked at each study and went through each and evaluated it. Honestly, they haven't found an inconsistent example where whiles she said that three years was a long followup in one study, but short in another. There is no inconsistency of that sort that they identified, and it is also useful in thinking about how consistent Dr. Moorman was in applying these criteria.

Think about the criticisms we heard about the Plaintiffs' forest plots. You heard from the Defendants, well, Dr. Moorman and Dr. McTiernan didn't highly value the Habel study, for example, the McGwin study, the MSK study, and all of those showed an increased risk. It's very indicative that different methodology is being applied honestly.

The reason for that is when you look at these criteria, those studies are not going to be considered of very high weight if you are applying it honestly.

Some things are really worth stopping and thinking about here. The Defendants have not said these are the wrong criteria. They haven't said that there is an important criteria missing from this, there should have been eight or nine, and it was actually more important than one of these. They agree these are very important criteria to consider for studies, she got the right ones.

So, really all of the action is at the next phase, the application phase, the weighting of the studies. These are the right criteria, it is consistent, but are they applied in the correct way.

I am going to get into the Defendants' critiques. The way I count them, I think there are six.

I'd venture to say these are really in the weeds. I think these are a little bit boring and the question you should ask is, is this really a Daubert issue or is this kind of a fight for the experts, but we can see as we go through them.

The first one is weighting methodology. I didn't hear much about today in the presentation. In the reply they really harped on it and said, did Dr. Moorman use the Newcastle or AHRQ criteria, or a weighting system of that sort, a methodology of that sort. Dr. Moorman answered, I don't know, I don't think so, not necessarily.

On redirect she basically agreed that she followed the same factors that those more formal systems agreed with, but,

you know, she didn't necessarily follow that exact system in that exact way, and there is no case that actually says one has to do that.

The Defendants experts didn't follow either of these systems, and there is no legal authority indicating that this is actually something that is required, and even if it were required, the criteria themselves are not in the record, but you can find them pretty easily online and confirm they are really the same criteria that I just laid out. Everyone agrees on the basic things that a study needs to have to be of more weight or less weight.

The next point that they say is that the weighting is inconsistent, and there are a couple of different points on this in the reply there was kind of a comparison of the Cardwell study, the Ronco study, and Norgaard. You saw a bit more of that in the slide presentation. How could you possibly reconcile these?

I am not going to go through every example, but I think the key thing is, if you are using multiple different factors, you can find inconsistency with respect to any one of them, and that is really not a problem at all.

For example, if you were doing a study of Ranitidine and you just had to take half a pill, for example, but you followed someone for a hundred years, it would be kind of ridiculous to weight that study at a very high level, but that

is exactly what you would say if followup were the only criteria.

Followup isn't the only criteria, you have to get a weighted average of all of the criteria to get a high weight. That is basically the way it works.

So, looking at Cardwell, Ronco, and Norgaard in particular, let's go through their criteria.

The first one, what kind of study is it? Cardwell studies nested case control, and that is also what Ronco is, and then Norgaard is a cohort study, okay. So, that tells you followup is going to be more important for Norgaard. There is not going to be sort of a direct analogy to followup for Cardwell or Ronco.

Then, number two, the study size, it is also important to think with the study size what the study is, because case control will have fewer participants necessarily, so that is why it is kind of more fair to look at the number of cancers rather than the number of participants because of the way the statistics work out when using a case control versus a cohort study, but they didn't emphasize the study size as being an important thing.

The third factor is the exposure, and here is where it really starts to become obvious why Dr. Moorman thought Cardwell was a better study than Norgaard. So, Cardwell had actual pharmacy records and details about what pills people

used, and that meant you could get a defined daily dose. They could bracket people into zero to 180 days, all the way up to more than three years because you had that data on the actual dose people used.

Norgaard didn't have any of that. What Norgaard had was two prescriptions and then up to ten prescriptions. They may have had a five prescription cut as well, but you don't know how many pills are in the prescription. You don't know the strength of the prescription, 75, 150, 300, and it is just basically true that ten prescriptions really isn't that many prescriptions at all, so it should be considered a very low dose study.

Then, with the Ronco study, you know, there is a bit of a difference when you are talking about a dietary study versus a pharmaceutical study because almost nobody, when they are talking about what they eat, they are filling out a questionnaire and they say, well, I have a steak about once a week. It would be a little bit ridiculous to think that was the only steak they ever had in their life, and next year they are going to have no steaks ever again. That is just not empirically the way people eat.

Dr. Moorman discussed that at page 49 of her report, Dr. McTiernan talks about that as well, that diets are very consistent over time, and that is absolutely not true for pharmaceutical drugs, and you can see that in the Adami versus

Norgaard, for example, that two-thirds of the cohort took only one prescription. You are just never going to get numbers like that in a dietary study.

That means that it makes sense to think of a dietary study as a longer term, talking about something that is more consistent over time, and you can make that assumption safely for dietary studies where you can't make it for pharmaceutical studies.

The fourth one is followup, and again, there isn't as much of a concern with followup for a nested case control study. Norgaard had 14 years. 14 years is a lot better than some of the studies that are at issue in this litigation, but it is not nearly as good as IARC suggests, which is 30 years if you're trying to say there is no risk of cancer.

It gets partial credit for that, but not a huge degree of weight, and that is what Dr. Moorman said as well.

And the fifth issue, misclassification, and here there is a serious concern over misclassification in the Norgaard study and there is less of one in the Cardwell study. The Defendants say, oh, nobody cares about misclassification, none of the study authors talk about that, but that is not true at all.

We cite it in our papers, and you can see when you read the studies that a bunch of them say the limitation is we weren't able to get over-the-counter drugs, we weren't able to

study them or track them, there might be a risk of misclassification.

Now, Cardwell dealt with this and said it's probably not a big problem because only ten percent of the drugs sold here are over-the-counter medication. Ten percent, you are probably not going to get a huge amount of misclassification just from that.

The Norgaard study in Denmark, as Dr. Moorman pointed out, it was 83 percent by the end of the study, 83 percent of Zantac was sold over the counter in Denmark. You are going to get a lot more misclassification, and so reasonably you give a little bit less weight to the study by Norgaard.

Last point, bias and confounding. Norgaard didn't track relevant features that you want for bias and confounding. It didn't have information about smoking or alcohol. It didn't have other information on obesity, for example, or other confounding factors that would be important, confounding factors that Cardwell did control for.

They say, well, there is only limited data for smoking, but they said they controlled for it. They had a lot of information, more than 80 percent of information on it, and they tried to control for it in other ways to guess at the 18 percent, 20 percent, whatever, they were missing, and Cardwell thought he had controlled for it.

Norgaard just has no information at all, and you can

say that an active comparator study is going to be better at controlling for bias than actually measuring the different confounding factors and statistically controlling for it, but it is certainly not crazy to think measuring for it and controlling for it statistically is a little bit better if you are trying to study something, and that is what Dr. Moorman reasonably concluded.

So, let's see. Yes, I think that is fairly obvious, just applying the criteria and going through them you can easily come to the conclusion that Cardwell is very good, Ronco is kind of in the middle, and Norgaard is not a very high weight, and there is no inconsistency in the principal example that they came up with.

They have on their slide 21 in their presentation and that say the Tran study and the Liu study didn't have very good information on bias and confounding, but if you actually read the slide, it is really not that bad actually.

It said it did control -- the quote on the slide said they did control for age, sex, smoking, and alcohol in the Tran and Liu study, and then the parade of horribles, the things they didn't control for was, "incomplete or unknown exposures." Okay, sure, could have been confounded by incomplete or unknown exposures, that is true of every study, but it is pretty good to have information on smoking and alcohol, and it wasn't unreliable of Dr. Moorman to say that that is worth a bit of

weight.

The third point the Defendants attack apart from the weighting is over-the-counter misclassification. They come close to saying this just isn't a thing, and they blame Dr. Moorman for not quantifying it, but she explained in her report, and they haven't really demonstrated why this is wrong, that if you don't have the data at all, there is no way to quantify the effect of the data.

Dr. Chan says he can, Dr. Moorman says that she can't. It is not the role on Daubert to say, well, actually there was a calculation that you could have performed as an epidemiologist to quantify this and you don't understand how to do it.

It is fairly intuitive and not unreliable to say if there is no information on the misclassification, there is no way to calculate the exact size of the effect. What you can do is, well, if it is 83 percent of the market it is going to be more of a problem than if it is ten percent of the market, and that is what Dr. Moorman reasonably concluded as to the Norgaard and Cardwell studies.

There was even less information for some of the other studies, so she flagged it as an issue that she considered and used it to reduce the weight of some of these studies.

Most of the studies affirmatively admit that this is a limitation, so she is definitely not out on a limb here.

On reply, on page 39, the Defendants come back and say Norgaard and Adami didn't think it was a problem and here is what they said. This is Norgaard. "Over-the-counter medication is more expensive. We would expect concomitant use of over-the-counter Ranitidine to be low."

This is kind of a weird thing to say when it is 83 percent of the market. It is more expensive, but it is still sort of dominates. That might mean there is something strange going on about the people that are purchasing Ranitidine in Denmark for at least certain periods of the study, but the authors don't say anything about that.

In my mind that is not really a sufficient response, and Dr. Moorman didn't consider it sufficient either. Adami says any bias would be limited because all major H2RAs were similarly impacted by over-the-counter use.

In the first place, this isn't true. It isn't true because Ranitidine is an older drug, and went OTC faster, so there is a reasonable chance that more people would have purchased it that way.

Also, you can look up statistics on what the market share is, and they could have done that instead of just assuming that it would be equivalent for all the different H2RAs.

There is sort of a deeper problem here. The deeper problem is there is an assumption that, well, if both of the

medications that you are comparing are sold over the counter, then there is no bias, but this doesn't make any sense. The concern is that some people in the H2RA group, and some people in the Ranitidine group are misclassified, meaning they didn't just take Ranitidine, or they didn't just take the H2RA.

Saying, well, true, some people need -- sure, A group may have also taken Ranitidine, but some people in the Ranitidine also took H2RAs, doesn't eliminate the bias at all. If what you are measuring on two arms of an active comparator study are two populations of people that took both drugs, you are just going to get a result that is biased toward the null. It doesn't wash itself out. They both independently would bias it toward the null because there is going to be less of a difference between the two arms of the study, so that response, as Dr. Moorman found, is not sufficient.

The fourth point that they raise is that active comparator -- the reasoning on active comparators, it doesn't withstand scrutiny. They spend a lot of time on this and really kind of miss a number of points that she made, but the response to it is on her -- in her rebuttal report on page 5, and she says, "my criticism of the active comparator studies were based on two broad concerns with the studies. First, key assumptions of the proper use of the active comparator studies were not met."

That is what you heard about, that was the only thing

you heard about, that premise, and I will talk about that in a little bit.

Then second, and we emphasize this in our brief, the active comparator studies had numerous other limitations and sources of bias, including an incomplete assessment of Ranitidine, misclassification of exposure, inadequate followup time, inappropriate study populations, for example, they are too young, lack of information on important potential confounders, and potential conflicts of interest. You have heard a lot about Adami, it's sort of a reference to that.

That list of criteria should sound familiar because it is the same exact weighting criteria that I have been talking about for this entire presentation.

The point is, even if Adami was not an active comparator study or Norgaard was not an active comparator study, there are completely different reasons that are independently sufficient why it should get less weight and that are fully consistent with her methodology and well explained.

Let me address the points that they made about why, they say, it is a proper active comparator.

Dr. Moorman gave two reasons. The first is evidence of increased risk, and on this, there is assure, and PPIs. They don't really say anything about PPIs. They basically seem to agree that PPIs do increase risk for cancer, and so that kind of leads to a question. So, what about all of those

active comparator studies with PPIs, are they biased to the null?

The Defendants don't seem to agree with that, but they stay pretty quiet on it, and there is good reason why they don't really talk about PPIs, because the Kim S study, for example, expressly says in the study, we didn't do an active comparator with PPIs because PPIs might be associated with cancer, and so did not conduct a study on PPI as an active comparator.

Then she cited a number of studies saying the same principles, the same mechanism, the same reason PPIs could cause cancer seems like it should apply to H2RAs and she explained what that mechanism is, and then cited a number of studies.

They really got pretty far into the weeds talking about each particular study and why actually if you look at it, it doesn't fully support it to the same extent. I really question whether at this point it is a Daubert issue. Does this make the analysis completely unreliable because on one weighting factor, talking about one reason why this active comparator study wasn't quite as good, she didn't do enough analysis in their view because five studies were not quite enough to say that one of the drugs was associated with cancer?

It seems like asking quite a lot for her to have done an independent Bradford-Hill analysis on every H2RA before

saying I have concerns about this, it is a reason to weight the studies a little bit less, which is really all Dr. Moorman said.

The next reason is the severity of the indications and how diseased the population is, and the Kim Y D study does support that, does say H2RA and Ranitidine population have different disease levels and that could make a differences.

At first, they basically join the party in saying the Kim Y D study is a very bad study, we agree with that, but i also misses the point because if the criticism is going to be analysis of Ranitidine over time, it doesn't necessarily mean that they get the population statistic about who smoked wrong.

That is kind of a more basic fact about the database that we would hope is still pretty accurate. The fact is the other database that they want to use, that they rely upon, didn't collect this information, so we can't really compare and see in Denmark is this actually true. Because the authors didn't collect the information this is one thing we have to go on, and it is a reason to think that other H2RAs are not an ideal active comparator.

And also, of course, Dr. Moorman cited FDA guidance in discussing this and the Defendants don't disagree that if she is right about the severity of the indications and the diseased populations, then it is a pretty good reason to discount the active comparator studies at least a bit.

The fifth point is the dietary studies, and there is a number of different attacks here. I heard a lot about Ronco and Keszei that I, frankly, was not expecting to hear. I didn't see any of that in the briefs and saw a number of things that were a little bit new about other things.

But one thing that stood out is, Mr. Brown said that Dr. Moorman had no testing data, that she has no basis for saying that any amount of NDMA in dietary studies is similar to any amount of NDMA in Ranitidine studies.

Your Honor asked about the GSK master data sheet. I believe that was one of the things we were supposed to be prepared to discuss. That is cited in Dr. Moorman's materials considered list.

It is really just not true that she didn't have access to information about the testing of Ranitidine and, you know, the FDA did release a bit more detail than just the top and bottom of the range for a bunch of different manufacturers.

So, she had a fairly reasonable basis to say that directionally the dietary studies were consistent with the amount of NDMA in Ranitidine, and that is what she said on page 45 of her report. The dietary studies, it's between 400 nanograms and 300 nanograms of NDMA, and that is comparable to the amount of NDMA in Ranitidine.

I understand Defendants want to say there is pretty much no NDMA in Ranitidine, something like that, but that is

not a reason to say that her estimate saying that these are reasonably comparable is unreliable since there is ample reason to think that Ranitidine is certainly over the minimum ADI that the FDA set, because otherwise it wouldn't have been pulled from the market.

So, the 30 to 400 estimate that Dr. Moorman talked about seems eminently reliable.

They also criticized saying some dietary studies quantified, some of them didn't quantify NDMA. A lot of the ones that did quantify NDMA got more weight, and Dr. Moorman explained that if it just looked at meat and didn't talk about NDMA that much, mostly just looked at it to say it is consistent with my argument, consistent with my opinions, not saying that it greatly adds weight to the opinions, and that seems about the right thing to do when you have a large volume of studies.

Some of them are stronger, and some are a little less relevant, but also some of the studies, even if they didn't precisely quantify NDMA, did talk about tertiles or quantiles and say that, well, if you had less NDMA versus more NDMA the risk increased. That is not the same as exactly quantifying it, but it certainly is suggestive of what happens as more NDMA is added to foods and you can still assume that, based on what the human diet is, it is not going to be wildly dramatically different.

You can say for a given study that looks at a given diet, the 25th percentile compared to the 75th percentile shows an increase. That is going to tell you something about dose and dose response that is helpful and that is also what Dr. Moorman did.

The last point that they attack is the Bradford-Hill analysis and they really focus on strength, dose response, and consistency, so I will try to hit each of those.

The first is the strength, and in the reply I got the sense that they just wanted Dr. Moorman to calculate a relative risk, just add everything together and then come up with a number that is the strength of the association with respect to each cancer.

That would really be false precision. There isn't a clear way, when you are talking about different studies, different methodologies, dietary studies, occupational studies, to say, you know, I think it is exactly 1.3, 1.6, something like that. It would be a little bit fake, a little bit unscientific. There isn't any way to calculate it like that.

What she did do is, for example, on page 108, she said, this is for bladder cancer, the relative risks reported in the studies described above were 1.11 to 1.56 for Ranitidine use, 1.2 to 2.82 for occupational exposure to NDMA, 1.12 to 2.16 for dietary NDMA exposure, and 1.2 to 1.47 in the meta analysis and cohort study of processed meat in relation to

bladder cancer.

This is about the strength of the association, and then she says these relative risks are of similar magnitude to several other exposure disease associations that are generally accepted to be causal associations as described in the introduction to the report, including oral contraceptives and breast cancer, menopausal estrogen and breast cancer, passive smoking and lung cancer, residential radon exposure and lung cancer, and Trichloroethylene exposure and kidney cancer.

What she is saying there is, here is the range and an exposure of that strength is very consistent with associations that are considered causal, and then gives specific examples, and that certainly is taking due account of the importance of the strength of an association.

Since the Defendants quoted Sir Bradford-Hill, it is worth quoting him back as well exactly on this point where he says in the very same lecture, people are too quick to dismiss a cause and effect hypothesis merely because the association is slight. There are many occasions in medicine when in truth this is so.

So, he is saying, yeah, if you have an association that is ten times, 15 times, that is pretty good, but if you have a smaller association, it's more in the range that Dr. Moorman just said for bladder cancer, that doesn't mean that it couldn't be causal, it certainly still could be causal.

The next point is dose response. She discusses dose response in detail. She cites a number of studies, dietary and occupational studies, but also Ranitidine studies that as NDMA risks go up, the -- as NDMA goes up, the risks go up for cancer, and that is all in the report in a lot of detail.

A big part of their attack here is talking about the minimum dose, and they say what would be the absolute minimum that could possibly cause cancer, and they sort of try to trick Dr. Moorman and say, well, could one pill do it? Well, it is a mutagen, it's a genotoxin. In theory one pill could do it, it could cause cancer, but, you know, could could mean something like there is a one in a billion chance. It is a very small chance, it is not a zero chance, but it is a very, very small scientific risk.

What she said is consistent with the best science, and as Dr. Moorman explained, genotoxins don't have a threshold, they don't have a minimum amount below which it is impossible that they cause cancer, but that is not quite the same thing that people mean in lawsuits when they say what is the minimum dose that can cause something.

Because the minimum dose that can cause something, if you were to say there is a one in a billion chance that this is going to and so it can cause, the Court would say, the jury is going to have to find this by a preponderance at some point, so one in a billion isn't really going to cut it even at the

general causation stage.

So, I'd venture that the statement is scientifically accurate, but it doesn't mean that Dr. Moorman is giving any possible exposure as the only way to get over the general causation jump.

Also, I would like to mention they didn't ask a question that would have been really, really easy and very relevant to general causation in this case, which would have been something like, you know, Dr. Moorman, would someone who took Ranitidine regularly for ten years get enough NDMA for that to cause cancer? And she would have said yes, and that certainly would be enough to get over the general causation hump as a legal matter. It isn't just about what the minimum possible dose is, but whether there are people that could have been over a dose that would cause cancer.

Also, the dose response in Cardwell, for example, after three years there is clear evidence of dose response, and none of the other studies even had detailed enough information to get that far.

So, a lot of the dose response information where they are saying Adami doesn't show it, and Cardwell doesn't show it, again, when you are comparing two prescriptions to ten prescriptions, that would be almost like saying, well, if you smoke 100 cigarettes versus 150 cigarettes next month, or over the course of two months, is there a dose response

relationship?

All you are really going to track is noise at that point, the amount is so low. Their chart said for ten years of pack a day smoking you are going to get a 1.2 increase. So when you are talking about doses this tiny, the dose response analysis is essentially meaningless, and that is what Dr. Moorman said.

She didn't rely on the Norgaard and Adami and all the other dose response sub analyses because the amounts are so low that you would not expect to find a dose response for Ranitidine given the science of how NDMA can cause cancer.

The third point is consistency and, you know, frankly, the studies here on Dr. Moorman's view and on Plaintiff's view, with the exception, probably, of the Kim study, the studies here really are consistent, and the reason the studies here are consistent is because a number of them simply aren't looking in a place where one would expect to find an increased risk of cancer.

That is true in the -- I keep going to the Adami and Norgaard studies, but they are good examples for demonstrating the point, but how about the Iwagami study, for example, where he had a 2.4 years of followup, and the median age was somewhere around 40. If you give someone Ranitidine or Nizatidine, it's hard to tell in that study, for just a year, maybe two years or less, and then followup for 2.4 years, you

are just not going to expect to find anything at all.

So, it is not inconsistent to say that there is a no association finding there, but there is a positive association when you look in this different way, and that indicates that there is a consistent finding, which is what Dr. Moorman did.

The last point I want to discuss is the case law, basically trying to apply the case law to the critiques that we heard from the Defendants and just say, are these Daubert issues, or are these issues for the jury?

The Eleventh Circuit case law such as Chapman and McClain say that you have to have at least one of three primary methodologies, epidemiology, dose response, and background risk.

You can also have a secondary methodology, a plausible biological mechanism, for example. We have a lot on that. The Defendants haven't really challenged how plausible the mechanism for cancer formation is. Animal studies, the Defendants haven't challenged that. Tissue studies, adverse event studies, haven't really challenged those, they actually do support it.

So, the only question is, is there at least one of the primary methodologies to sort of hook on the secondary methodologies to say that there is at least a reliable opinion? We'd certainly say that the answer here is yes.

So, look at the examples in the case law where there

wasn't enough. McClain, it was ephedrine and caffeine no epidemiology at all and a pharmacologist and treating physician testified in that case and they cited no studies. They just relied on general hypotheses about what ephedrine and caffeine might do in combination.

They weren't even particularly plausible hypotheses because ephedrine and caffeine are in hundreds of consumer products all over the place, and there really isn't any evidence that they do cause strokes or the other medical issues in that case.

This case really isn't anything like that. There certainly are some studies and there certainly is some calculation of background risk, for example.

What about Chapman? In Chapman they looked at calcium zinc in Fixodent, and again, no epidemiology at all, no dose response, no background risk. They said they didn't know, couldn't calculate those things.

Instead, what they tried to say is, based on what we know about zinc, you know, probably if you have too much zinc you will get not enough copper in your body, and then once you have not enough copper, it causes other conditions, and they didn't have any other studies demonstrating any individual link in the chain.

To make things worse, the information they had about zinc wasn't even about calcium zinc, it wasn't even about the

relevant type of zinc that was in the Fixodent product. That was why they were out in Chapman.

Here, the Defendants are not saying there is no epidemiology. They are not saying there is no dose response and they are not saying that there is no background risk. They are just saying the studies that they like are better and actually counteract the studies that the Plaintiffs like such that you can't come to an opinion at the end of the day, but that is fundamentally not a Daubert question.

One last thing. The only case that they have where there actually was a study is the Allison versus McGhan case, but there there were 19 studies that went against Plaintiffs and the Plaintiffs claimed four that were in support, but three were about something else entirely, and then there was one study, just one, with a 1.24 relative risk, and the expert said, ah-ha, one study, this is it, we have causation.

But he didn't explain why the one study was any better than the 19 studies. He didn't have any plausible explanation of why it could possibly outweigh the 19 other studies, and the Eleventh Circuit said, in a case that extreme you can't just say without any explanation why you valued that one over the other, and I would suggest that we are nowhere near that here.

Here there are studies on both sides, and with respect to every single study an explanation in Dr. Moorman's report, based on her criteria, explaining this is why I say this study

isn't worth very much, this is why I say this other study is worth more, and they don't say the criteria are bad. All they say in an incredibly detailed presentation is trying to fight each one.

That really runs headlong into Schultz, a Seventh Circuit case that we quoted. Rule 702 does not require or even permit the District Court to choose between two studies at the gatekeeping stage, doesn't require it, doesn't permit it, but bringing things a bit closer to home, what about the Abilify case?

Here is a quotation from Abilify on 1372: To the contrary, a District Court may not evaluate the credibility of opposing experts or the persuasiveness of competing scientific studies. That is quoting the Eleventh Circuit case Quiet Technology versus Hurel-Dubois.

Again, you can't compare the persuasiveness of studies at Daubert it is supposed to just about is there no epidemiology, is there no dose response.

Roundup is exactly the same. In Roundup there were a bunch of cases -- a bunch of studies on Monsanto's side, a couple of studies on the Plaintiffs' side, and Judge Chhabria said, you know, as -- with a quotation from Daubert, this is shaky, but admissible.

Judge Chhabria also said something else. He said, maybe in the Eleventh Circuit, under McClain, this could be a

challenging thing, but you know who disagreed with that? The Ninth Circuit disagreed with that.

If you look at Hardeman versus Monsanto, which is that case on appeal, at pages 961 to 962, the Ninth Circuit says, McClain, we agree absolutely with McClain. There is no difference in the standard in the Ninth Circuit compared to the Eleventh Circuit, and then affirmed Judge Chhabria saying, using the same standard that would apply in the Eleventh Circuit this was absolutely the right way to do it.

Mr. Petrosinelli for the first time, this never appeared in their briefs, says Roundup, that case is inconsistent with the Eleventh Circuit, that it wouldn't come out the same way here, and their reasoning first is based on something Judge Chhabria said that the Ninth Circuit disagreed with, and I will trust the Ninth Circuit on that question.

Then also said there is a difference because in Roundup they talked about, the way the Plaintiffs framed it here, is there a realistic dose, the Plaintiff with the best case could possibly say it causes their cancer, and the Defendants say that is just not the case here, in the Eleventh Circuit you have to have the minimum dose, but this really doesn't make any sense.

What that means is, if you can't calculate the exact minimum dose threshold, even if you are totally above any plausible threshold, you are going to be thrown out on general

causation, and that doesn't make any sense in an MDL where there are going to be people who have had 20 years of exposure, people who have five years of exposure. It is just going to be about can you calculate the exact minimum dose.

That is not faithful to the general causation inquiry. They also say, it is not even something the Eleventh Circuit has ever said. McClain and Chapman were both cases about specific Plaintiffs. The also had specific causation at issue and so the analysis blended a little bit.

The concern in those cases, and really what they are getting at is, if you can't show that the Plaintiff had above a minimum dose that would cause it, then you get thrown out at general causation, and that is probably true. If the minimum dose is something like you have to have a thousand pills of Ranitidine every day, yes, that is not going to quite cut it, but that is not the same as playing gotcha games on calculating the minimum dose, when clearly someone who took ten years of Ranitidine would be well over.

So, the basic question when you consider the critiques against judge -- against Dr. Moorman is whether this case is with Abilify and Schultz and Roundup, where there are different studies with and different levels of persuasiveness, or if this a case like McClain or Chapman or Allison where all the evidence is on one side. There is no epidemiology, there is no dose response, and there is no assessment of background risk.

Respectfully, I would submit, your Honor, when you look at the degree of effort that they are putting in to discuss each study and say the way that they weighted this particular study is wrong, they are really talking about persuasiveness, they are really talking about something that is not a Daubert issue at all, that is only an issue for the jury.

*THE COURT:* Okay, thank you very much.

Were we able to mute the person? We have control of that?

All right. Now the concluding portion of the Plaintiffs' presentation.

*MS. LUHANA:* Good afternoon, Judge.

*THE COURT:* Good afternoon, almost good evening.

*MS. LUHANA:* Good to see you. Roopal Luhana for the Plaintiffs.

Judge, I am addressing the majority of the Plaintiffs' response to Defendants' motion to exclude Dr. Salmon's general causation opinions. My colleague, Mr. Nigh, will address some other points at the end of my presentation on Dr. Salmon as well.

I feel compelled to raise that, unfortunately, Defendants have raised specific arguments in their presentation today that were never raised in their brief.

We believe Defendants waived these arguments and should be precluded from raising them, as you instructed in

your order.

You received my slide presentation yesterday which was responsive to the Defendants' briefing to exclude Dr. Salmon; however, I do not plan to go through the majority of my slides in an effort to address Defendants' new arguments that completely conflate issues and misrepresent what Dr. Salmon did, and I have actually incorporated some of the Defendants' PowerPoint slides into my presentation.

We will rely on our briefing to address the crux of Defendants' arguments in their brief.

So, let's start with Dr. Salmon's qualifications.

Can we go to the next slide.

Dr. Salmon is a heavily credentialed toxicologist, he has a BA, an MA, a Ph.D from the University of Oxford with a focus in biochemistry.

He has over 30 years of experience at the EPA. His life's work has focused on leading health hazard and cancer risk assessments, conducting dose response assessments and carcinogenic potency modeling, developing guidelines for cancer risk assessment methodology.

That is in line with what he did here for his report. He did a qualitative and quantitative assessment on NDMA and the NDMA in Ranitidine specifically.

Despite his qualifications, Defendants say he is not qualified to review the epidemiology. Defendants cite no case

law to support their position, nor could they. Dr. Salmon testified that he routinely evaluated epidemiology in conducting hazard assessments at the EPA.

For example, when you assess carcinogens you are looking at animal studies, you are looking at mechanistic data, you are looking at the epidemiology, and he testified that he routinely did that. He has also authored epidemiological articles.

Next slide.

Tellingly, in McClain the Eleventh Circuit upheld the District Court's decision to exclude a non-epidemiologist because he didn't review epidemiology. Clearly Dr. Salmon is qualified to review epidemiology and appropriately did so here.

Next slide, please.

So, let's go through his methodology.

Next slide.

Dr. Salmon searched and reviewed over 1100 scientific publications. He then discussed each piece of relevant evidence in an over 240 page report in detail. He assessed, he analyzed, and he discussed strengths and weaknesses individually of each piece of evidence. He applied the Bradford-Hill considerations thoroughly to conduct a weight of the evidence analysis where he reviewed all of the relevant evidence, including studies that were statistically significant and those that weren't for his Bradford-Hill guidelines.

He conducted a separate quantitative dose response assessment where he used statistically significant studies to do his dose response assessment, and his dose response slopes. This is in fact, Judge, the standard that is set up by the WHO and IARC.

Ironically, Defendants criticize Dr. Salmon for doing things inconsistently outside of litigation versus in the courtroom, when in fact he was extremely consistent.

Go to Defendants' slide 3. Next slide.

So, on one hand, Defendants state that Dr. Salmon, outside the litigation relies on statistically significant studies, indicating that that isn't something he did here, and then here, they say in his report that he is cherry picking and stacking the deck because he is using statistically significant studies for his dose response calculations. Defendants' position simply doesn't make sense.

On this slide, Judge, on the left-hand side is a chapter that Dr. Salmon wrote, that is published. It is a summary of the IARC guidelines describing what is considered sufficient evidence from human studies.

The quote here, though, is taken out of context because if you look at the rest of the quote, it goes on to state that epidemiological investigations are complex and they are sometimes insensitive, and therefore you need to take into account case reports and mechanistic evidence to come to

causality assessments.

On the right side, Judge, is page 11 of his report where Dr. Salmon is in fact citing to Bradford-Hill. The sentence that is actually omitted, Dr. Salmon says, Hill expressly warned that too much focus is spent on statistically -- statistical significance and the value of P, such that no significant difference was dangerously being interpreted as no difference, and thus a reasonable approach is necessary to interpret the data and weigh the evidence whatever the value of P.

So, this is exactly what Dr. Salmon did for his Bradford-Hill analysis, he considered and weighed each and every study.

Importantly, Defendants are complaining what Dr. Salmon did for his Bradford-Hill analysis was his dose response calculations. What Dr. Salmon did here, his analysis is reliable, it's robust, it's complete, and consistent with his experience and his expertise as a toxicologist.

Next slide, please. Next slide.

So, Dr. Salmon conducted a quantitative dose response assessment. He identified source data, he scoured all available studies and data to find where NDMA exposure was specifically quantified and cancer association was studied. He calculated lifetime cumulative exposure based on study parameters to ultimately calculate the amount of NDMA exposure

that was associated with a particular cancer.

He calculated a dose response curve based on the statistically significant diet and occupational studies, and the he calculated dose response assessment and tied it to the NDMA exposure levels found in the FDA the Defendants and Emery's testing, which ultimately showed that Ranitidine users are exposed to enough NDMA in their Ranitidine pills to cause each of the five designated cancers.

Judge, Dr. Salmon was so thorough that he reviewed every study that discussed NDMA, and to the extent that the study quantified NDMA dosage and assessed association of cancer he included it in his report.

So, Defendants' criticisms about him omitting studies are clearly misplaced. So, let's take a look at the next slides, which are slides 6 and 7 from Defendants' presentation.

So, Dr. Salmon's discussion of all the studies confirms that he did not conduct dose calculations because the data wasn't there.

So, let's go through some of these studies that are grayed out.

Look at the Straif study and go to his report, page 56. He says he didn't quantify NDMA exposure specifically because exposure levels were only calculated at high, medium, low, or had missing data, so he was unable to do the calculations.

Then you look at Vlaanderen, which was a rubber worker study, and once again nitrosamine levels were not estimated. Then you go to De Stefani 2012, it's a case control cancer study that didn't report NDMA intakes. You look at Gonzalez, that is page 64, the study authors didn't report NDMA intakes, so he couldn't do the calculations.

So, while Dr. Salmon discussed all these study findings for his Bradford-Hill analysis and weighed all these studies and discussed them in detail at length, he couldn't do the dose calculations because the data wasn't provided in the study.

Go to the next slide.

So these studies on the right, Dr. Salmon didn't admit any of these studies. He discussed them and included them for his Bradford-Hill analysis, but he didn't include them for his dose response assessment because that is not the WHO standard methodology. These were studies that quantified NDMA and he did those calculations, but they weren't statistically significant.

So, here they say that Dr. Salmon said the results are uninformative. I want you to look at that testimony, 188:12 to 191:17. There he testifies that the studies are informative in so many other ways, but not for dose response calculations.

Go to the next slide, so slide 8. Okay, go forward. Sorry. Thank you.

As I stated earlier, while Defendants haven't criticized Dr. Salmon's dose response calculations until today, they previously conflated concepts with his dose response curves. While the Defendants criticized Dr. Salmon for using statistically significant studies to calculate the dose slopes, and quantify the amount of NDMA exposure necessary to cause a statistically significant increased risk of cancer, they cite to no support for that, their position.

In fact, their position is contradicted by the standard that calculates dose response curves. The WHO specifically spells it out and says for dose response you should do exactly as Dr. Salmon did.

You use the best representative study to calculate risk to use statistically significant study results to calculate dose response assessment. It's right there, you take a reliable study, it has to be identified, where the exposure of the study population can be estimated with acceptable confidence and cancer incidence is statistically significant and you choose the best representative study.

That is exactly what he did, he used a reliable methodology established by WHO.

Defendants, unfortunately, continue to conflate concepts, and I don't know if it is because it's lawyers interpreting science, but that is not what Dr. Salmon did. He reviewed and assessed and analyzed all the studies, and then he

did a separate quantitative analysis, a dose response calculation specifically as WHO directs.

Next slide.

Similarly, the IARC program of chemical safety provides that dose response relationships should be supported with statistically significant differences. So Dr. Salmon assessed and analyzed literally all the studies, as I said, for his Bradford-Hill analysis; however, for his dose response assessment he used statistically significant studies that are consistent with standard methodology.

Next slide.

Then Defendants attack Dr. Salmon for pooling the dose response slopes together, which is truly a red hearing. Defendants don't raise what impact his illustrative slope averages had on his dose response assessments because while he presented those averages as illustrated and as a hypothetical, he didn't use them for his dose response assessment.

Also, while the Defendants call it an unprecedented methodology, if you look at Exhibit 84 that they provided, that discusses how the EPA pools elevated tumor incidents for same cancer sites. So, here they criticize Dr. Salmon for pooling the averages together, but he did that to show an illustration of what the slopes are it you just calculate the mean.

In fact, Dr. Salmon, for his dose response assessment, he used the individual statistically significant dietary and

occupational studies for his analysis.

Go to the next slide.

So this, Judge -- go back, go back to that pooling.

So this is once again Defendants' slide, and you will see he calculated the individual dose response slopes for each of these statistically significant studies, and then he did a mere calculation of the mean slope. So he was showing that, he didn't use the mean slopes for any of his analysis for his dose response calculations.

On the right-hand side he provided a hypothetical, and this is more so for specific causation down the road. If you had individuals who were taking Ranitidine for ten years and each pill has 1,000 nanograms, how much would the hazard ratio increase for those pooled cancers.

He testified this was a hypothetical, this is just illustrative. I am not using this for my dose response calculations to tie it to the actual amount of NDMA in these Ranitidine pills, which is what he did.

He looked at the testing, he looked at the diet and occupational studies, assessed the increased risk of cancer and what amount of NDMA it took to get there, lifetime cumulative exposure, and then he tied it to the actual NDMA that was being found in these pills, and that was at various points.

That was at baseline based on NDMA levels found in Defendants' own testing, as well as Emery's testing, and then

looking at it after zone exposure testing to introduce it to the elements when people are opening their pills and they expose them to heat and humidity, and seeing what the rise is.

He did all those calculations in his chart to show that the levels that you are seeing in these pills -- the levels that you are seeing in these diet studies and occupational studies are equivalent to the levels that you are seeing in the Ranitidine pills. That is what the chart is all about.

Go to the next slide.

And this is what I was raising in terms of -- this is De Stefani in 1998, where Dr. Salmon went about and did the individual dose calculation for this study.

Go to the next slide.

So, Judge, on this slide they say Dr. Salmon is on an island of his own, and here he is saying that there is clear evidence of does response and citing Cardwell.

That is the only Ranitidine study that he says provided dose response. Dr. Moorman's and Dr. McTiernan's quotes are in agreement on Cardwell and the other Ranitidine studies.

If you take a look at Defendants' cite, where they got these quotes from, if you look at the complete quote they go on to say, yeah, the Ranitidine studies don't show dose response except for Cardwell. You don't see he that on the screen here,

however it is noted.

In addition to that, every other study that he is saying is clear dose response, he is relaying on the diet and occupational studies, and not the Ranitidine studies.

I am going to turn it over to my colleague to make some final points. Thank you for your time, Judge.

*THE COURT:* All right. Okay, four minutes.

*MR. NIGH:* Good afternoon, Judge, may it please the Court.

I will address a few issues regarding Dr. Salmon with the balance of our time, and we are not going to use any slides, but I wanted to address some of the new issues that the Defendants have raised for the very first time here today. It is not in their briefing, and I will address some of those issues.

First, Defendants use a graph on Ranitidine dose response addressing dose response in Ranitidine studies. That was never presented in any briefing or any expert report and it is very misleading.

First, it attempts to put DDD, defined daily dose, on the same horizontal access as number of prescriptions, but is woefully inaccurate and doesn't appear in any expert report, nor would it.

At the top, the DDDs don't even match the Cardwell study. Cardwell had 366 to 1,095 DDD, and 1,096 plus. They

don't have those numbers at the top, they have 730, not 1,095. This is important.

Next, on the scale Defendants attempt to equate ten prescriptions with 1,095 DDD. That is wrong. We don't know the length of the prescription or the strength of the prescriptions in Adami or Norgaard, but if each prescription was for only one month for 150 milligrams, then at ten prescriptions, that would only have a DDD of 150. That is nearly ten percent of the 1,095 DDD, yet in that chart it attempts to equate the two.

Now, the purpose of that is, that is nearly ten percent of the 1,095 DDD, and on the dose response chart, that finding from Adami and Norgaard should have been at the very start of the DDD response in Cardwell, between 1 to 182.

Looking at that, it would have made it clear that all the dose response results for Adami and Norgaard would be shrunk and compressed to the far left on that dose response chart, and then it would highlight precisely what Dr. Salmon stated when he stated that the Ranitidine epidemiology studies, that of them only Cardwell for bladder cancer had enough information to do a dose response analysis for Ranitidine studies.

He also did a dose response analysis from the NDMA studies.

Finally, Defendants attempt to include Iwagami for all

cancers on that same dose response chart. That study can't be used for dose response for Ranitidine. Nearly 60 percent of the users in Iwagami used Nizatidine and that analysis is a dose response analysis combined for Ranitidine and Nizatidine. It doesn't tell us the dose response information for Ranitidine.

Next I will address some criticisms raised by the Defendants for the very first time regarding Salmon's calculation of a lifetime cumulative exposure. These criticisms are not in their papers and they should be waived, but I will address them.

Calculating lifetime cumulative exposures based on statistically significant results only is not cherry picking. That is how lifetime cumulative exposures are supposed to be done, and that is actually more conservative than including non-statistically significant results. It would take less time to reach those results.

Now, Defendants also want to blame Salmon for not doing a meta analysis, but this is also disingenuous for three reasons.

Meta analysis for these types of data would have been inappropriate, and if Salmon did it, they would have complained that he did it, because doing a meta analysis on different study designs at different end points would be inappropriate.

Finally, just a couple of more points. Doing a meta

analysis for a lifetime cumulative exposure analysis is not required.

Just like Defendants have cited no legal authority or even any scientific authority for nearly all of their criticisms of Salmon's meta analyses that they are raising for the first time here today, Defendants have cited no legal or scientific authority regarding this issue.

This hearing is the first time Defendants raised the allegation that a meta analysis for a lifetime cumulative exposure analysis is required and Salmon avoided this, just like this hearing is the first time the Defendants chose to raise nearly all of their allegations regarding Dr. Salmon's lifetime cumulative exposure analysis, and therefore these arguments are waived and should not be considered.

*THE COURT:* Okay.

*MR. NIGH:* We will also rest on the papers related to Le and Michaels, and any rebuttal regarding those two experts should be disallowed. Thank you.

*THE COURT:* Defendants have ten minutes left for your rebuttal.

*MS. CANAAN:* Your honor, can we ask for a five-minute break?

*THE COURT:* Yes. We will be in recess until 5:20 or so.

(Thereupon, a short recess was taken.)

*THE COURT:* Okay. Your rebuttal.

*MR. HOLIAN:* Thank you, your Honor.

*THE COURT:* Ten minutes, right?

*MR. HOLIAN:* I don't think I will need to take that, your Honor, it should be less.

I want to make four points. First I want to address right up front this notion of waiver, that we have somehow waived arguments about Dr. Salmon.

I was listening very closely to the Plaintiffs to hear what it was they thought was new. It wasn't that we moved on dose response, that is in pages 57 to 59 of our opening brief. It is not our criticism of Dr. Salmon for relying on dietary and occupational NDMA epidemiology. That is on page 57 of our opening brief.

It can't be that Dr. Salmon relies on Dr. Najafi's testing, because that is in the testing motion where we moved to exclude any expert who relied on it.

I think what seemed to strike a nerve was the graph where I showed what the dose response data looked like. Your Honor saw that data dozens of times today in different ways on forest plots. It is on many, many, many of the experts' reports, including theirs. It is just a different way to show what a dose response curve should look like if there is consistent evidence of a dose response and contrast that to what it does look like here. It is lawyer argument, but it is

throughout the record.

This point about meta analysis is simply responding to one sentence in the Plaintiffs' opposition where they said, oh, no, people combine things all the time, they do meta analysis, in defense of what Dr. Salmon did.

There is no waiver here of any of the arguments that I made today, your Honor.

Second point, dose. I want to draw things back a little bit. You heard a lot of information about all these studies, but I think one thing that we have been crystal clear about as the Defense is the importance of dose, both a threshold dose and dose response.

Dr. Salmon is the only one who has suggested that the Ranitidine epidemiology establishes a dose response, and he is the only one who has purported to do any calculations to show what the threshold dose is at which you should start to see an effect. Drs. McTiernan and Moorman did not claim there is any threshold dose, you saw that in their testimony, and they did not claim that the Ranitidine epidemiology establishes a dose response.

Without a threshold dose, the Plaintiffs can't meet the call in McClain that an expert has to say how much is too much. Again, it doesn't have to be incredibly precise, 3.2 years of exposure at 873 nanograms, but it has to be something more than long-term use.

Without a dose response, which McClain says is the hallmark of general causation in a toxic tort case, the Plaintiffs can't reliably use the Bradford-Hill criteria to conclude general causation.

So, because Dr. Salmon is the only one who purports to identify a threshold dose and the only one arguing that the Ranitidine epidemiology establishes a dose response, his exclusion is fatal to the Plaintiffs' general causation arguments.

Third, you heard Ms. Luhana discuss the standards that Dr. Salmon referenced and saying it is perfectly acceptable to only look at statistically significant results when you are trying to assess a dose response, but those guidelines that she cited, one slide was from the World Health Organization about how you derive air quality guidelines.

The other was the IPCS guidelines on environmental toxicology. Those are guideline values that environmental toxicologists, which is what Dr. Salmon is, those are guidelines they use to figure out, using the worst case assumptions, what is the highest level to which people can be exposed so that we can be sure below that there is no risk of harm.

The Eleventh Circuit has made clear that is totally different than what you do in a toxic tort case where the question is not what is the dose at which there isn't harm; it

is what is the dose at which there is harm. In McClain, the Eleventh Circuit has been clear, a Court performing the function you are should not mix those two things up, they are very different standards.

By the way, if you read those two documents carefully, they actually endorse the importance of statistical significance in deriving reliable conclusions. For example, in the IPCS document that Plaintiffs' counsel cited, the very next sentence says, if you have results that aren't statistically significant, then that suggests the level of exposure is, quote, "without biologically significant adverse health effects."

So, don't confuse Dr. Salmon porting in environmental toxicology risk assessments, precautionary regulatory standards, with the Court's role here.

The last thing that I want to do is draw the lens back a little bit from the blizzard of data and information you heard today. I want to talk about one thing you didn't hear today, which is the Plaintiffs coming forward and identifying anybody else in the world who has concluded that Ranitidine causes cancer.

The cases talk about general acceptance is relevant factor under Daubert, and it not just the general acceptance of methods, it's are these conclusions accepted because, as the Advisory Committee notes to the 2000 amendments to Rule 702, if

an expert purports to use a method that is generally used, like weight of the evidence or Bradford-Hill, but reaches a conclusion that nobody else has reached, then a Court sitting where your Honor is, applying Rule 702, should suspect that the methods were not faithfully applied.

That is exactly what has happened here. The case law is clear that the words weight of the evidence and Bradford-Hill are not magic talismans that the Plaintiffs' experts or the Plaintiffs lawyers can invoke and thereby shield themselves from any scrutiny by the Court.

The Court, in exercising its gatekeeping role, has to look carefully at whether those methods were reliably applied, and here they were not.

The FDA has looked at this issue and it has spoken in peer reviewed literature. The EMA has looked at this issue and it has spoken. They have both concluded the evidence does not reliably establish that Ranitidine causes cancer. The peer reviewed scientific literature has examined this question over and over and over, and not once in a peer reviewed study has anyone concluded this establishes that Ranitidine causes cancer.

So, this is not a case where we need information to fill in the gap. The only people in the entire world who say Ranitidine causes cancer are the experts retained by the Plaintiffs, and the Court should not allow a jury to

second-guess the decisions of FDA, EMA, and the rest of the scientific community.

The Court should exercise its gatekeeping function and conclude that the Plaintiffs have not faithfully applied -- Plaintiffs' experts have not faithfully applied the weight of the evidence or Bradford-Hill methodology and it should grant our motion and exclude them under Rule 702.

Thank you, your Honor.

*THE COURT:* Thank you very much.

That is all of the formal presentation for the day. I want to thank everyone. Clearly a lot of hard work and effort went into it. They were extremely helpful, so thank you to everybody who presented and all of those who helped in putting together the presentation.

On the agenda we did leave a line there that I may take some time to ask questions, and I also put aside tomorrow morning before the first set of motions are being argued.

I am going to use a little bit of the time now, I hope not too much, because it has been a long day. I know are all tired, so bear with me for just a few questions. They may not be all the questions.

Whoever you think is most appropriate to answer the question can come forward. Even if it is more than one person, that is fine, just state your name on the record when you come forward so we get who is answering the question.

This is just kind of housekeeping. I know that in one of the inquiries I made, both the Plaintiffs and the Defendants emailed me kind of a chart on study duration and sample size. So I want to thank you for that.

Is there any reason why I could not ask you to have that filed on the docket, notice of filing, so that I have it formally as part of the record? Would that be acceptable to the Plaintiffs?

*MS. FINKEN:* Yes, your Honor.

*THE COURT:* From the Defense?

*MR. CHEFFO:* Yes, your Honor.

*THE COURT:* That was easy. Okay. This I sort of alerted to as well, one of the topics, so this is for both parties. Defense first, since they were your motions today.

In your view, what is the current opinion of the FDA and the EMA on the dangers of Ranitidine? What document or documents should I look at to locate that opinion?

I would ask everyone, try to answer the question, and if you have to explain, you can explain, but I know we are trying to keep it -- does that sound familiar -- try to keep the answers as brief as possible. I am not looking for argument as much as kind of the information.

*MR. CHEFFO:* Yes, your Honor. To try and be brief, there was a quote that I put up that I think does state the most recent FDA pronouncement. Also, the Florian study is an

FDA study and I think that is there. I am not aware that they have done anything to say anything inconsistent with that, and I think the same is true for the EMA slide that we put up.

*THE COURT:* So whatever FDA and EMA slide you used, as well as the Florian study, would be, in the Defense's view, the opinion of the FDA and the EMA generally, including on the dangers of Ranitidine.

*MR. CHEFFO:* That's correct, your Honor.

*THE COURT:* Thank you. From the Plaintiffs.

*MR. RONCA:* Jim Ronco for the Plaintiffs, your Honor.

So, the product it still off the market. You could look at the EMA report from 2020, however, five of the most important studies were not yet published, so they didn't have them.

In addition, we don't think you can look at Florian because they did not do a complete review. They are talking about a couple of sentences in an article on the urinary content of NDMA, and Florian didn't comment on seven of fourteen Ranitidine specific studies regarding cancer.

*THE COURT:* All right. So this will be for Defendants first.

This has to do with the 5912-5, that document which I know I put you on notice that I wanted to ask about, and I received word that it was fine, even though it is a sealed document. Can I get confirmation that discussing that document

is not a problem from Defense?

It was in the list of topics that I had circulated.

*MR. CHEFFO:* Yes, your Honor, that is fine to discuss it.

*THE COURT:* Okay. Okay. So, in the Plaintiffs' response, the Plaintiffs cite to this document and I just want to make sure I am reading the document correctly. So, if we look at the document -- do you have that in front of you?

Does Defense have it in front of you?

*MR. CHEFFO:* I don't, your Honor, but I think I know what you are talking about.

*THE COURT:* You might need one of these to read it, a magnifying glass.

*MR. CHEFFO:* I am sure I will need that as well, your Honor.

*THE COURT:* Tell me when you have it.

*MR. CHEFFO:* We can try and find it. The other suggestion, obviously you are the Judge, but if you'd like us to get it and be prepared to discuss it first thing in the morning, I can do that, since I don't know if I have it here right now.

*THE COURT:* Okay, that is fine.

Let me let you know what the questions are if you want to make note of them. It looks like the document memorializes GSK tests of both API, that is raw product used to make

Ranitidine and Ranitidine that was made from the API, and the tests were for NDMA.

So, that is my first question, am I correct, yes or no, and do you need to explain anything?

So, do you need me to repeat that question?

*MR. CHEFFO:* No, I think I got it.

*THE COURT:* The next question is, there is a column -- let me get it in front of me.

There is a column that reads: API NDMA content, and I want to just confirm that that reflects the results of the API tests for NDMA. That's the next question.

Then relatedly, there is a column entitled Product NDMA Content, and I want to confirm my understanding that that is the results of the Ranitidine pills for NDMA content that were made from the API.

My next question is, why are there columns with a strike through the data? So, there is like a strike through on some of the columns and I want to know why. And then I wanted to know -- this really is a question for both sides, so both sides should take note.

I suppose, you know, if the Plaintiffs have a different view of the answers that the Defendants give tomorrow, you should be prepared to tell me why.

The other question is whether the parties would agree that as a general matter the tested API resulted in a higher

NDMA number than the tested Ranitidine, and if you don't agree with that statement, I would like to hear why.

And then I would like to hear an explanation on why the tested API would have or could have resulted in more NDMA than tested Ranitidine pills from the same API.

I guess relatedly, just an understanding of why was the document made and is there anything further that you want to tell me about it that would help me understand it.

Okay, so we can get answers from that.

*MR. CHEFFO:* Thank you, your Honor, for that opportunity. We will be prepared tomorrow for that.

*THE COURT:* Okay. Let's see here.

While we are on charts, let's move to another one for a moment.

This has to do with the Dr. Salmon chart on page 223 of his expert report dated January 24, 2022. So, I think this would best be directed to the Plaintiffs initially, and I know a couple of you spoke about Dr. Salmon's chart. Feel free if you need to share in the answer.

So, the Plaintiffs, in your opening introduction, showed this slide, I think it was number 59, and it summarized, as you explained, Dr. Salmon's dose response analysis. I want to make sure I understand it.

The chart comes from page 223 of the Salmon expert report. Do you have that in front of you? Do the Plaintiffs

have that in front of you?

*MR. NIGH:* Yes, your Honor.

*THE COURT:* That was Mr. Nigh for the record.

So, as I understand it, and this is a question to have you confirm if I am right or not, the first column on the chart labeled Study Cumulative MG, milligrams, comes from page 221 of the expert report. On page 221, Dr. Salmon uses data from Loh, De Stefani, Keszei, and Hidajat. Am I correct so far?

*MR. NIGH:* Yes, your Honor.

*THE COURT:* As I understand it, what Dr. Salmon is estimating is the amount of NDMA one would have to consume to have a substantial measurable increase in risk from NDMA.

Is that correct?

*MR. NIGH:* As pertaining to those specific dietary studies. He also did a dose response analysis across all the studies, but as pertaining to those specific dietary studies in Hidajat --

*THE COURT:* Right. I should have asked the next sentence. He is using data from those studies to compute the number?

*MR. NIGH:* That is correct, your Honor.

*THE COURT:* So, in other words, you have confirmed that everything I said was correct, so does that mean, for example, that one would have to -- looking at that first column, one would have to consume, for example, 3.2 milligrams

of NDMA in order to have a risk of gastric cancer, and that is based upon data contained in the De Stefani study?

*MR. NIGH:* Somewhat, with a little bit of a nuance. They he would have to consume 3.2 milligrams of NDMA to have a statistically significant increased risk of 2.07, as seen in the dietary studies. It doesn't answer the question of at what lower level could there still be increased risk. He has other analysis for that.

*THE COURT:* Okay. With respect to the second column that is labeled FDA Max, as I understand it, does this column use the highest amount of NDMA that the FDA detected in its tests, that is .31755 milligrams? Is that correct?

*MR. NIGH:* He defines FDA max as the highest amount of products that was intended for the U.S. in testing by the Defendants or the FDA. There are obviously other test results, and he explains as to why he looked at highest, other test results in other countries that were much higher than that testing for the Defendants and the FDA, baseline testing.

*THE COURT:* And going on from there, using that number, he then goes on, does he, to figure out how many years it would take to reach the measurable significant increase in cancer risk that is in the first column?

So, in other words, it would take 10.08 years to reach the significant level contained in the first column for gastric cancer. Is that accurate?

*MR. NIGH:* Yes, if you only look at baseline levels of the pristine product tested by FDA and Defendants.

*THE COURT:* Now, the third column, as I understand it, uses the average amount of NDMA that Emery Pharma found, and then using that number, just like the FDA max number, figures out how many years one would have to consume Ranitidine to get to a significant cancer increase. Is that correct?

*MR. NIGH:* The significant cancer increased risk in the study. So he does again in the -- he has other analyses that show lower increased risk, but for that study, that is the amount.

I do want to add that that is just based on Emery Pharma's baseline testing, opening up the bottle, test the pill, none of the other consumer experience issues.

*THE COURT:* Okay, thank you.

The fourth column, am I understanding that this column adds NDMA to the FDA's max tested NDMA based upon consumer storage testing? Is that correct?

*MR. NIGH:* Yes, and specifically he used the more conservative zone analyses, even though those numbers were much lower than the additional amount seen in the bathroom, sun, and shade testing, and he explains that, and he explains that this was done for general causation purposes.

*THE COURT:* So, in other words, that comes from page 218 of the report where he looks at, just as you said, zone

storage testing from Emery Pharma because the FDA did not conduct zone storage testing. Is that right?

*MR. NIGH:* Somewhat, mostly. The FDA did do some stability testing later, that is what led to the recall in April 2020, but for the most part he did that testing because the FDA didn't publish those results and the Defendants have not done that testing whatsoever.

*THE COURT:* Based upon that data from Emery Pharma, is it correct that Dr. Salmon concludes that the NDMA in a Ranitidine pill would be increased by a multiple of 2.5 to account for NDMA generated from heat and humidity?

*MR. NIGH:* Yes, just relying on the zones. He also calculated previously that it would be even higher if you look at the bathroom, car, sun, shade, and shower.

*THE COURT:* That is why, turning back to the chart, the NDMA in the fourth column, .79 milligrams per year, is 2.5 times higher than the NDMA in the FDA max column, column 2. Is that correct?

*MR. NIGH:* Yes, your Honor.

*THE COURT:* So .79 milligrams per year is 2.5 times higher than .31755. Is that correct?

*MR. NIGH:* Yes, your Honor.

*THE COURT:* The fifth column, this column, is it correct, adds NDMA to the Emery Pharma NDMA average column, the third column? Is that correct?

*MR. NIGH:* Sorry, I lost where you were.

*THE COURT:* The fifth column, it appears -- let me tell you what I think, and you tell me if I'm right. This column adds NDMA to the Emery Pharma NDMA average column, the third column. This time Dr. Salmon is using a number 2.25 milligrams per year, and I think that number, correct me if I am wrong, comes from page 220 of his report where he references testing that Dr. Najafi did, and based upon that testing, Dr. Najafi found an average amount of NDMA from consumer storage testing.

Dr. Salmon then -- he takes Dr. Najafi's numbers, converts them into an amount of milligrams per year, and that is how we get the fifth column. Is all of that correct?

*MR. NIGH:* That is accurate, yes, your Honor.

*THE COURT:* So, it appears to the Court that the studies that Dr. Salmon has relied upon to construct this chart are very much intertwined with the Defendants' Daubert motions.

For example, the first column, study cumulative milligrams, the amount of NDMA necessary to result in a measurable cancer risk increase, comes from the dietary studies in Hidajat, the occupational study, but the Defendants have argued, among other arguments, that no reliable methodology in this case, in this MDL, could use those studies, that is the dietary studies and the occupational Hidajat study, to form a causation opinion.

I am going to ask both sides, this is hypothetically, if the Court were to agree with the argument and conclude that the dietary studies and the occupational studies could not be a part of a reliable methodology, what is the Court to make of this chart? Does it become unusable because the entire chart is premised upon the dietary and occupational studies?

I would like to get the Plaintiffs' view on that, and then I have the flip side of that for the Defendants.

*MR. NIGH:* In the context of dose response, dose response is oftentimes looked at in a toxic tort on the carcinogen itself.

So, we would state that that is a different question than how epidemiologists weigh various studies.

If your Honor were to rule that the dietary and occupational exposure studies couldn't even be used for that purpose, then this chart would not be relevant; however, he did also calculate a cumulative dose response specifically for bladder cancer based on Ranitidine epidemiological studies.

*THE COURT:* Similarly for the Defendants, if the Court were to conclude that the dietary studies and Hidajat study can be a part -- is considered by the Court as a part of reliable methodology, would the Defendants agree that at least that column of the chart would survive their Daubert challenge as to Dr. Salmon?

*MR. HOLIAN:* No, your Honor, we would not, because

what Dr. Salmon is doing here again, he is cherry picking a single NDMA epidemiological study to do these calculations. He is picking the very best result that he want to pick. He is using Hidajat for three of these cancers.

If the Court were to hold, yes, you can extrapolate from the dietary and occupational studies, that still doesn't mean you can only pick the one that gets the best result for you. On top of that, it is also, in our view, unreliable to take the absolute highest result that the FDA got, that .31755 --

*THE COURT:* I will get into that in a moment.

*MR. HOLIAN:* So, you can't cherry pick within the dietary and occupational and you can't cherry pick the exposure that you're looking at in order to add those numbers together.

The last thing I'd say, your Honor, is sometimes these calculations get cloaked in mystery. If you look at this, the first column and the second column, all Dr. Salmon is doing is dividing the study cumulative milligram in that first column by .31755, all the way down.

I believe Mr. Nigh said that it is unscientific to do calculations that way, and we agree.

*THE COURT:* Okay. Now, a related question to the Plaintiffs' first, the chart uses data from Emery Pharma, from Dr. Najafi, which is also the subject of a Defendant Daubert challenge. If the Court were to grant that motion and exclude

Dr. Najafi from testifying, does that mean that the column about Emery Pharma becomes unusable?

Similarly, the column on consumer storage testing, which comes from Emery Pharma, becomes unusable?

*MR. NIGH:* Your Honor, I'm sorry, I missed a piece of that. There are a lot of moving parts.

*THE COURT:* Do you want me to say it again?

*MR. NIGH:* Yes.

*THE COURT:* A related question, the chart uses data from Emery Pharma, from Dr. Najafi, which is also the subject of Defendant Daubert challenge.

If the Court were to grant the motion and exclude Dr. Najafi from testifying, does that mean that the column about Emery Pharma becomes unusable?

Similarly, would the column on consumer storage testing, which comes from Emery Pharma, become unusable?

*MR. NIGH:* It is difficult to answer that in a vacuum because, as we will discuss tomorrow, there are a lot of other data points that could also be used and are consistent with Dr. Najafi's results, that demonstrate that as they are exposed to more heat and humidity, we see additional amounts of NDMA. That is een even in Sanofi's own testing.

*THE COURT:* But if Dr. Najafi is not -- does not survive, that was the premise of the hypothetical, so not just as to the storage, but I know you are going to discuss other

things tomorrow with respect to Dr. Najafi, but I am --

*MR. NIGH:* My point is, there would still be support for some of these numbers other than FDA max that are part of the record, other than Najafi's testing.

*THE COURT:* Other than Najafi's testing, all of his testing.

*MR. NIGH:* Yes.

*THE COURT:* Okay. Did you want to add something?

*MS. LUHANA:* Yes. Judge, I would also note that the Defendants have done significant testing, and we will talk about the master data spreadsheet tomorrow where you will see values that are way above 435 nanograms that meet these parameters.

In addition to that, the root cause analysis, Defendants did test the pills, two batches, at extreme temperatures, well, some were high temperatures, and with humidity, and we can discuss those results as well, which get us to these points that Dr. Najafi has come to without Emery's data.

*THE COURT:* Thank you. Same question on the flip side for the Defendants, if Dr. Najafi -- if the Daubert motion as to Dr. Najafi is denied, do the Defendants agree that at least the columns of the chart based on Dr. Najafi's data would survive their Daubert challenge as to Dr. Salmon?

*MR. HOLIAN:* No, we wouldn't, because you have to have

a hypothetical on top of a hypothetical. You have to agree you could use the dietary and occupational NDMA epidemiology to start this chart at all.

So, if the hypothetical is they get past that and Dr. Najafi also doesn't get excluded, there is still a great big problem with this chart, which is, if this is a reliable way to look at the data, then why doesn't it show up in the Ranitidine epidemiology?

In that far right column, the number of years it takes under his analysis to show a significant risk in the increase of gastric cancer is 1.4 years, and the highest time period is liver cancer, 6.5 years. That is well within the followup time, the exposure analysis, everything else in the Ranitidine epidemiology we have seen.

So there, your Honor, I'd say it can't be reliable to cobble dietary and occupational epidemiology with max FDA tests, cobble it with Dr. Najafi's testing and say, ah-ha, we have a dose response and a dose threshold, because it is not in the Ranitidine epidemiology.

If you have epidemiology answering the question that is the center of this whole case, you can't just say cast that aside, cobble together these other things in order to derive a general causation opinion, particularly because you don't even get to the dose response part of the Bradford-Hill analysis unless the Plaintiffs first prove a statistically significant

association that is free of bias, which they haven't done.

*MR. NIGH:* Your Honor, may I respond to one small point in that statement?

*THE COURT:* Yes.

*MR. NIGH:* The statement that it is not consistent with the Ranitidine epidemiology literature, I think the Defendants are conflating followup and usage dramatically here. Those are two separate issues, and those compound along with the other issues that we discussed.

In terms of liver cancer, a Ranitidine epidemiology study that discusses a median of 6.5 years, where is that? On the flip side, bladder cancer, there is a study that shows a statistically significant increased risk at three or more years, or 10,095 DDD, which actually might be a little higher than three years.

What do you see there? The result is consistent, 3.86. None of the other Ranitidine studies have that sort of use to show that consistency.

*THE COURT:* The Plaintiffs aren't suggesting, though, in any way that this chart uses Sanofi data; is that correct?

*MR. NIGH:* This chart does not use Sanofi data.

*THE COURT:* Okay. So, the chart uses an average value from the Emery Pharma tests, and I understand that an average value may be an appropriate, or a reasonable number to use in these sorts of calculations, but the FDA number used on the

chart isn't an average, it is a maximum value.

As the Court understands it, the FDA tests resulted in a range of numbers. Is it the Plaintiff's position that the causation question in this MDL may be premised not on an average value of those tests, but a maximum value?

*MR. NIGH:* That is only part of the premise. The other part of the premise is that the -- these levels from the FDA are only the baseline testing on pristine product. We are going to demonstrate that. Later, the FDA demonstrated that there was significantly more NDMA that is forming after their baseline testing. That is what led to the recall in April 2020.

In addition to that, there are all sorts of other test results that may not have been the specific Ranitidine specifically designed to go to the U.S., but they also demonstrate much higher levels, and they are relevant to the question, they are the same compound. So, that was all part of the thought of using that number.

*THE COURT:* So, then, are the Plaintiffs saying that it is plausible to assume that what you have referred to, I think certainly today, what you call the therapeutic dose, the highest dose that a Plaintiff could have received in this case, flowed from the maximum value and not the average value?

*MR. NIGH:* That is not -- the FDA max is not saying that at all. The FDA max is chosen, realizing those three

issues that I just explained previously. So, it is not based on a legal standard.

It is based on those three issues that, one, the FDA, when they did additional testing that led to the recall of all Ranitidine in the United States, that was after their baseline testing. They found excessively more NDMA. That is what led to the recall in the United States.

Two, there are all sorts of testing on product that wasn't designated for the U.S. that we know, but shows much higher levels of NDMA on the same molecule.

So, those are the sorts of issues why I would say that that is not necessarily the maximum result or the highest level.

*MR. HEINZ:* Your Honor, it is also important to keep the legal question in mind here. This would be deciding the case for every Plaintiff in this MDL, and so following the Plaintiffs' framing of the general causation question, the highest sort of plausible or realistic dose anyone could have, the question is, could any Plaintiff have had a consistent number of pills with 800 nano grams of NDMA?

If that is even plausible, we should be given the opportunity to try to prove that, even if the Court concludes that we would need to make an additional evidentiary showing on that point.

*THE COURT:* Okay.

*MR. PETROSINELLI:* Your Honor, that is totally wrong. That is not the legal standard in the Eleventh Circuit, but unless you want to hear that now, I will save that until tomorrow.

*THE COURT:* We will save that for tomorrow, something to look forward to. I am going to wind down. I just have a couple more.

This is for the Plaintiff. The Defendants have cited to or quoted a couple of times, I have one time, but I think it was two times, that things that the Plaintiffs have said in their briefing -- the Plaintiffs' motions, which we are going to hear next week, so one example is on page 67 of Docket Entry 5868, and I don't expect you to have right at your fingertips.

It reads: Plaintiffs' general causation theory in this litigation is for long-term use of Ranitidine. The claim is not that Ranitidine causes cancer after one dose or even a year's worth, but over many years of regular use, and it goes on.

So, my question is: Do you agree that I can rely upon those statements even though you made them in your motion when I am considering the Defendants' motion?

I guess it would be vice versa, if I can rely upon something the Defendants may have said in response to your motion in their motion, but it arose today in the context of statements that the Plaintiffs made in their motion.

I want to get your position that you don't disagree that I could rely upon this is something the Plaintiffs have said, albeit in their motion, when I am considering the Defendants' motion, and the Plaintiffs' position vis-a-vis the Defendants' motion.

*MR. HEINZ:* Your Honor, at previous hearings you said that an LDC member could give an answer, and then if it is wrong, can be rescued.

*THE COURT:* This is your free pass. Do you want to take a stab at it?

*MR. HEINZ:* I'll give a free pass answer, and then if Mr. Gilbert or Ms. Finken disagree, they can swoop in.

Certainly the briefing began as a unified whole, there are a number of cross references, and sometimes even citations to exhibits, and so there is certainly no intent to take an inconsistent position, and as far as the record, we would say, you know, you could consider both of them holistically.

As far as the judicial estoppel question or something in there, I don't have a clear view on that. I do think, you know, it would be potentially a little unfair if in fighting for general causation where there might be a conflict of interest with a particular Plaintiff who has maybe a theory that is not mainline, it might be a little bit unfair to hold that against them, but that might need to be briefed at a later point.

*THE COURT:* Okay. I am trying to understand the answer. I can use what the Plaintiff said or not?

*MR. HEINZ:* You can use it to the same extent as if it appeared in the briefing for this motion.

*THE COURT:* All right. Anybody standing up to -- no supplement. Okay. You did well, no swooping in.

So, again for the Plaintiffs, in your opening introduction, or maybe two of your slides cited to, I think, the Wagner study that I think it was published after the general causation expert reports were rendered in this case, and I think you might have even noted that.

But I want to make sure you agree that I can't consider a study when it didn't form the basis of any expert's opinion, and no one has moved to amend expert reports or things of that nature. Would you agree with that, from the Plaintiffs.

*MS. FINKEN:* Your Honor, are you referring to the Wang study?

*THE COURT:* Maybe the Wang, it was 2020. It wouldn't have been 2022, it was 2020. I don't remember what screen it was. You know what I am speaking about, and would you agree that your experts didn't rely upon that, and therefore I can't really consider it?

*MR. HEINZ:* Yes, and I don't believe it was cited in a report, it has not yet been published. If it were to be

published, we might try very quickly to move to supplement, but the limited point for which it was put forward was just this is sort of fast developing, and nowhere near as settled as far as what the outside experts beyond the litigation have concluded, and for that limited purpose.

As far as acceptance, we think you can consider it just because it goes to rebutting the Defendants' arguments rather than something that the expert herself relied upon.

*THE COURT:* To clarify, I can or cannot consider it?

*MR. HEINZ:* Our position is you can --

*THE COURT:* Do you have an argument separate from the study in other words that you are using in your rebuttal? The study, which isn't finalized and hasn't been relied upon by any of your experts, I can't rely upon it.

*MR. HEINZ:* That is right. The limited point for which we cited it was something like this is not a settled issue, and it is sort of atmospherically relevant to the extent you might otherwise think that some of the issues are settled, but certainly not as a basis of any expert's opinion.

*THE COURT:* Okay. It was Wang, and it was 2022, so I got the year wrong and the name of the study wrong.

*MR. CHEFFO:* Your Honor, I think the answer to that was they agree you can't rely on it, it wasn't published, it hasn't been peer reviewed, it hasn't been relied on by the experts.

*THE COURT:* Right. To the extent the Plaintiffs have another support for that argument, I suppose you will point te Court to whatever support at some point. I am not going to rely upon Wang 2022 for that proposition.

*MR. HEINZ:* Yes, your Honor.

*THE COURT:* For the Plaintiffs, Defendants made the point that in other studies that Dr. McTiernan has authored or coauthored she used followup times that were shorter than the followup times in the Ranitidine epidemiology studies.

I wanted to know if you have a response to that.

*MR. RONCA:* Your Honor, Jim Ronca for the Plaintiffs. In 400 studies, you could find some studies that are shorter and some studies that are much longer. I think they cited to three.

You could do the same thing with how statistical significance, 0.05, or confidence levels are dealt with. Because you have coauthors, you have journals with different requirements, so could you find some studies where they might have said if it is not statistically significant, there is no association. You could find the opposite.

I know in our briefing we pointed out that there were times when Dr. Chan, for example -- I think we pointed out five examples where he had a result that was not statistically significant that he called an association in his studies. We throw that around a lot, his study, her study.

Sometimes you are the senior author or sometime you are the first author, sometimes you are very involved, sometimes you are only applying data. To pull three studies out of the air and say this is inconsistent with everything she has done -- she has done 400 studies, she was cross-examined for 11 hours. If that is the best you've got, it is not that much.

*THE COURT:* Would your answer be the same for Dr. Moorman?

*MR. NIGH:* Your Honor, I would add one more thing. It was also a one dimensional examination, only looking at followup. We didn't look at the other issues that may have made it a more reliable study.

*THE COURT:* I was just asking about followup. I recognize that. Would it be the same general answer on Dr. Moorman as well?

*MR. HEINZ:* Yes, your Honor, with a modification that it is 150 instead of 400. I will say I don't specifically recall the examples being in the brief, so we didn't have time to canvass the 150 to find counter examples.

To the extend the Court finds that to be a particularly persuasive bit of evidence, we might ask to be able to look that up and give counter examples if it wasn't in the briefing, but we think the correct response is that it really isn't very probative.

*THE COURT:* This will be my final question for this evening.

For the Plaintiffs, earlier in the presentations Plaintiffs made the representation that Dr. McTiernan did not rely upon a crude number in the Norgaard study even though she had the opportunity to do so. I think the argument by Plaintiffs was, and I may be paraphrasing, if Dr. McTiernan wanted to cherry pick the data, she would have relied upon the crude number, which was higher, but instead she relied upon the adjusted number, which was lower.

You might need to take the evening and get back to me tomorrow, but I wanted you to show me, if you could, where in her expert report she states that she used the adjusted non-crude number. From my review, she seems to reference both numbers when discussing the study, that is the Norgaard study, but does not clarify which number was the one she used for her analysis.

I wasn't able to find anything on this topic in her deposition either. Is that something you could look at, unless you know the answer?

*MR. RONCA:* I don't know the answer off the top of my head, your Honor. We will look at it tonight, but the argument was in response to what the Defendants said, but I will look at it tonight.

*THE COURT:* Okay. You will be happy to know we will

call it an evening. That might cut out some of the question time for tomorrow. So, maybe for those of you who are presenting, and you think you are starting at 10:00 for your presentation -- I know you will be here at 9:00 anyway, but we might start your presentation a little early.

It sounds like Defense is going to get back to me on answers to that question about that one chart, and if the Plaintiffs have any followup on what I just asked, and if I think of another question or two between now and tomorrow, I might have another question or two.

I suspect we should be able to start the presentations a little earlier than 10:00. Again, tomorrow we are starting with the remaining expert motion, which is at 5696.

So, with that, you all are really anxious to go. You are all standing, let the record reflect, and have a nice evening. Go get something to eat and relax everybody, and get a good night's sleep.

(Thereupon, the hearing was concluded.)

* * *

I certify that the foregoing is a correct transcript from the record of proceedings in the above matter.

Date: September 24, 2022

/s/ Pauline A. Stipes, Official Federal Reporter

Signature of Court Reporter