UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA

In Re: Silicone Gel Breasts Implants Products Liability Litigation

BRADLEY CAGLE, as Administrator of the Estate of TONI J. CAGLE, and BRADLEY HOUSTON CAGLE, JR., an infant under the age of fourteen, by BRADLEY CAGLE, his father and natural guardian,

Plaintiffs,

v.

THE COOPER COMPANIES, et al.,

Defendants.

CASE NO. CV 96-6545 AHM (RNBx)

RULINGS ON DEFENDANTS' MOTIONS *IN LIMINE* AND ORDER GRANTING DEFENDANTS' MOTION FOR SUMMARY ADJUDICATION

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I. Introduction

Toni Cagle was diagnosed with breast cancer approximately fourteen months after receiving breast implants. Her breast cancer later caused her death. Her husband Bradley Cagle ("Plaintiff"), as the administrator of Toni Cagle's estate, alleges that her implants manufactured by The Cooper Companies, Inc., Surgitek/Medical Engineering Corp. (a subsidiary of Bristol Myers Squibb Co.), and Foamex, L.P. ("Defendants") caused or accelerated her breast cancer. He alleges that Defendants are either the manufacturers or the successors in interest to the manufacturers of the devices implanted in Mrs. Cagle. His First Cause of Action is for "Strict Products Liability." The others are as follows: (2) "Failure to Warn"; (3) Breach of Implied Warranty; (4) Breach of Express Warranty; (5) Fraud/Intentional Misrepresentation; (6) Negligence; (7) Loss of Consortium; (9) Wrongful Death; and (10) Pain and Suffering.[1]

This Order addresses four motions *in limine* filed by the Defendants and Defendants' motion for summary judgment. The *in limine* motions seek to exclude the testimony of Plaintiff's four causation experts. Those experts are Dr. Neugebauer (an epidemiologist), Dr. Batich (a polymer chemist), Dr. Lappé (a toxicologist) and Dr. Shanklin (a pathologist). Defendants' motion for summary judgment argues that because Plaintiff's experts are not qualified and the science they rely on is unsound, Plaintiff cannot demonstrate that Cagle's implants caused or accelerated her breast cancer. In his Opposition to the summary judgment motion, Plaintiff's attempt to demonstrate a genuine issue about causation is

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[1]This order does not address the claim, in the Eighth Cause of Action, brought by Cagle's son Bradley Cagle Jr. ("Bradley Jr."). Bradley Jr. was conceived shortly after Toni Cagle received her implants. After he was born, Cagle nursed him at her breasts. Bradley Jr. alleges that Defendants' conduct caused him to be exposed to a toxic chemical and that he "will be caused to fear and suffer future injuries the extent of which are unknown." Am. Compl. ¶ 114.

based exclusively on the experts and scientific data at issue in Defendants' motions *in limine.* Therefore, whether plaintiff can defeat the summary judgment motion turns on the extent to which Defendants' motions *in limine* are meritorious.

This case is different from most other breast implant cases, because Plaintiff is not alleging that Cagle's cancer was caused by silicone. Cagle was one of a relatively small number of women whose implants were coated with a polyurethane foam ("PUF"). Plaintiff alleges that PUF breaks down *in vivo* into 2,4-toluene diamine ("TDA") (also called 2,4-diaminotoluene), which he claims is carcinogenic. Am. Compl. ¶ 43. Plaintiff alleges that TDA from Cagle's implants caused or accelerated the progression of her disease. *Id.* ¶¶ 40, 48.

More specifically, Plaintiff's causation theory is as follows (the relevant expert is indicated in parentheses):

(a) One epidemiological study provides "suggestive evidence" of a causal link between PUF-coated implants and cancer (Neugebauer);

(b) The polyurethane coating of PUF-coated implants biodegrades after implantation in humans (Batich);

(c) The degradation products of the PUF-coating include TDA (Batich);

(d) TDA is known to be carcinogenic in animals and is a "probable" human carcinogen (Lappé and Shanklin);

(e) The amount of TDA likely released from Cagle's implants, Cagle's pregnancy (which began almost immediately after implantation) and the rare type of breast cancer Cagle suffered renders it more likely than not that her tumor was caused or its growth accelerated by TDA released from her implants (Lappé and Shanklin).

Having analyzed Defendants' challenges to the expert testimony of Lappé and Shanklin, I conclude that Plaintiff is unable to offer scientifically reliable evidence to support proposition (e). Therefore, even assuming that the evidence proffered to support propositions (a) through (d) is admissible, summary adjudication is appropriate, because Plaintiff cannot establish that breast implants caused *Cagle's* cancer. This Order nevertheless addresses the content and admissibility of the evidence proffered to support propositions (a) through (d), in

the event that on appeal the analysis and conclusion concerning proposition (e) is deemed incorrect.

Section II provides the relevant background facts specific to this case. Section III provides an overview of the legal and scientific principles applicable to evaluating the relevant scientific evidence. In Sections IV through VII, I evaluate each expert's qualifications and testimony based on the legal and scientific principles elaborated in Section III. Finally, Section VIII concludes that because Plaintiff's expert testimony that Cagle's cancer was caused by her implants is not admissible, summary adjudication in favor of Defendants is appropriate.

II. Background[2]

Defendants either manufactured or are successors in interest to companies that manufactured "Meme" polyurethane foam ("PUF") coated breast implants. After the FDA requested data from the manufacturers about the chemical composition of PUF and safety testing data on that foam, the manufacturers suspended shipments of polyurethane-covered breast implants in May 1991. Lappé Opp. Exh. A at 8 ("Lappé Expert Report"). At that point, the FDA estimated that approximately ten percent of women with implants had the PUF-coated type. *Id.*; Kern *et al.*, *Carcinogenic Potential of Silicone Breast Implants: A Connecticut Statewide Study*, 100 Plastic & Reconstructive Surg. 737 (1997) (SJ Mot. Exh. 22).

On May 2, 1989, Toni Cagle, a registered nurse, received two PUF-coated breast implants. SJ Opp. Exh. 3 at 17:20-23, 22:1-3, 25:11-13, 26:1-6 (Cagle Depo.); Am. Compl. ¶ 38. Cagle was 30 years old at the time.

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[2] The background facts are either undisputed or are construed in Plaintiff's favor, as required on Summary Judgment.

Cagle testified that before receiving the implants she had been "overly cautious" in conducting self-breast examinations. She testified that she had examined her breasts every two to three weeks and that she had never detected any lumps or other problems with her breasts. SJ Opp. Exh. 3 at 28:16-29:12 (Cagle Depo.) Before receiving her implants, Cagle's plastic surgeon examined her breasts and reported that he had found no masses. *Id.* at 28:1-5; Shanklin Opp. Exh. F at 67 (Patient History and Physical Examination Report). After Cagle received her implants, she continued to routinely examine her breasts. SJ Opp. Exh. 3 at 29:13-16 (Cagle Depo.).

Within one week of receiving her implants, Cagle became pregnant. SJ Opp. Exh. 3 at 27:4-5 (Cagle Depo). On June 16, 1989, Cagle's obstetrician conducted a prenatal physical examination and found no tumors in Cagle's breasts. Shanklin Opp. Exh. G at 70-71 (Prenatal Record).

At the end of June or the beginning of July 1990 – fourteen months after receiving her implants – Cagle discovered a lump in her right breast during one of her routine breast self-exams. Shanklin Opp. Exh. H at 113:21-114:15 (Maguire Depo.). She obtained a biopsy 451 days after receiving her implants on July 26, 1990. Shanklin Opp. Exh. F at 69. The resulting pathology report, dated July 30, 1990, reported "two portions of bright yellow firm tissue measuring 2.5 x 1.5 x 1.3 cm and 3.5 x 2.3 x 1.3 cm." *Id.* Exh. J at 83. The diagnosis was infiltrating ductal carcinoma, the most common type of breast cancer, accounting for up to eighty percent of all breast cancers. *Id.*; Shanklin MIL Exh. 3 at 163:3-164:7 (*Brusca Daubert* Hearing) & Exh. 4 at 28:8-20 (Bylund Depo.).[3] By the time the

[3] In Plaintiff's Opposition to the motion *in limine* to exclude Shanklin's testimony, Shanklin testifies that after his deposition he examined tissue slides from Cagle not previously available to him and has since determined that Cagle's cancer was actually a squamous cell carcinoma of the breast, which is "one of the most rare and one of the most aggressive cancers of the human mammary gland." Shanklin Opp. Exh. B ¶ 6 (third Shanklin Decl.). *See* Section VII.C.2, *infra*.

lump was diagnosed, the cancer had metastasized and spread to her lymph nodes. SJ Opp. Exh. 3 at 39:5-7 (Cagle Depo.). She underwent a mastectomy, radiation, and chemotherapy, *id*. at 35:11-12, but her cancer recurred and she died on July 26, 1993, at the age of 33 – approximately 4 years after receiving the implants and 3 years after being diagnosed with breast cancer. Shanklin Opp. at 4.

Cagle's family has a history of cancer. Cagle testified that she had a maternal half-aunt who contracted breast cancer and had a mastectomy, SJ Opp. Exh. 3 at 9:13-16 (Cagle Depo.), that her mother died of kidney cancer, *id.* at 8:17-19, and a paternal aunt contracted stomach cancer. *Id.* at 11:6-17. One of Cagle's experts, Dr. Lappé, has also reported that Cagle's maternal grandfather had a gastric carcinoma (stomach cancer) and a paternal uncle had some unspecified type of cancer. Lappé Expert Report at 6.

III. Legal and Scientific Principles Applicable to the Expert Testimony in This Case

Once someone is qualified as a scientific expert, his testimony is generally admissible under Federal Rule of Evidence ("FRE") 702 if it satisfies two criteria. First, the testimony must reflect "scientific knowledge . . . derived by the scientific method." *Daubert v. Merrell Dow Pharms. Inc.*, 43 F.3d 1311, 1315 (9th Cir.), *cert. denied* 516 U.S. 869 (1995) ("*Daubert* II") (quoting *Daubert v. Merrell Dow Pharms. Inc.*, 509 U.S. 579, 590 (1993) ("*Daubert I*")). This requirement "establishes a standard of evidentiary reliability." *Daubert I*, at 590. Second, the proposed expert testimony must be "relevant to the task at hand," meaning that it "logically advances a material aspect of the proposing party's case." *Daubert II*, at 1315 (quoting *Daubert I*, at 597).

The proponent of the expert testimony has the burden of establishing by a preponderance of the evidence that the admissibility requirements are met. Fed. R. Evid. 702 Advisory Committee's Notes. A trial court's decision to admit or

exclude expert testimony is reviewed under an abuse of discretion standard. *Gen. Elec. Co. v. Joiner*, 52 U.S. 136, 138-139 (1997).

A. Qualifications

A witness can qualify as an expert on the basis of "knowledge, skill, experience, training, or education," Fed. R. Evid. 702; *see also U.S. v. Cambindo Valencia*, 609 F.2d 603, 640 (2d Cir. 1979), and such qualifications are construed broadly. *Thomas v. Newton Int'l Enterprises, Inc.*, 42 F.3d 1266, 1269 (9th Cir. 1994); *Pride v. Bic Corp.*, 218 F.3d 566, 577 (6th Cir. 2000). A court abuses its discretion when it excludes expert testimony solely on the ground that the witness's qualifications are not sufficiently specific if the witness is generally qualified. *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 754 (3d Cir. 1994) (abuse of discretion for trial court to preclude trained internist with broad experience in field of toxic substances, who had spent significant time reading literature on the effect of PCBs on human body, from testifying as to whether PCBs caused illness in plaintiffs, even though witness lacked expertise in other, more relevant, specialized fields). A lack of specialization affects the weight of the expert's testimony, not its admissibility. *Holbrook v. Lykes Bros. S.S. Co.*, 80 F.3d 777, 782 (3d Cir. 1996).

B. Reliability

Although there is a presumption of admissibility, *Daubert I*, *supra*, at 588, FRE 702 imposes a "gatekeeping" duty on district courts to ensure that testimony based on scientific, technical, or other specialized knowledge rests on a reliable foundation. *Id*. at 597; *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 141-42 (1999). "[T]he trial judge in all cases of proffered expert testimony must find that it is properly grounded, well-reasoned, and not speculative before it can be admitted." Fed. R. Evid. 702 Advisory Committee's Notes. "The trial court's gatekeeping function requires more than simply 'taking the expert's word for it.'" *Id*. (*citing Daubert II, supra,* at 1319). In addition, "any step that renders [the

expert's] analysis unreliable . . . renders the expert's testimony inadmissible. This is true whether the step completely changes a reliable methodology or merely misapplies that methodology." *In re Paoli, supra*, at 745. In *Daubert I*, the Supreme Court articulated the following factors that bear on the reliability inquiry: (1) whether the theory or technique used by the expert can be or has been tested, (2) whether the theory or technique has been subjected to peer review and publication, (3) the known or potential rate of error of the technique or theory when applied, and (4) the "general acceptance" of the theory or technique in the scientific community. *Daubert I*, *supra*, at 593-94. These factors are not definitive or exclusive of others. *Id.*

In addition, courts have also found the following factors relevant in assessing the reliability of expert testimony: (1) whether the expert is proposing to testify about matters growing directly out of independent research he or she has conducted or whether the opinion was developed expressly for purposes of testifying; (2) whether the expert has unjustifiably extrapolated from an accepted premise to an unfounded conclusion; (3) whether the expert has adequately accounted for obvious alternative explanations; (4) whether the expert is being as careful as he would be in his regular professional work; and (5) whether the field of expertise claimed by the expert is known to reach reliable results for the type of opinion offered. Fed. R. Evid. 702 Advisory Committee's Notes.

At issue in these motions *in limine* and the summary judgment motion is whether Plaintiff's experts can present reliable evidence of causation. To prevail on his claims, Plaintiff must show both *general or generic causation* (*i.e.*, that PUF implants have the capacity to cause breast cancer in humans) and *specific causation* (*i.e.*, that Cagle's breast cancer was caused by her PUF implants). *In re Hanford Nuclear Reservation Litig.*, 292 F.3d 1124, 1133-34 (9th Cir. 2002). To demonstrate general and specific causation, Cagle's experts rely on animal studies, differential diagnosis and epidemiological studies. The Court will

discuss each such category of evidence.

1. Animal Studies

Animal studies may be admissible to demonstrate general causation. According to the *Reference Manual on Scientific Evidence* (Federal Judicial Center 2d ed. 2000) ("*Ref. Manual*"), in extrapolating from animal data, "one can usually rely on the fact that a compound causing an effect in one mammalian species will cause it in another species. This is a basic principle of toxicology and pharmacology." *Id.* at 410. Indeed, extrapolations to humans from animal experiments that involve significantly higher doses of the agent at issue are commonly used in the regulatory arena. *Id.* at 409. *See also* Cornell University, Program on Breast Cancer and Environmental Risk Factors in New York State, Fact Sheet No. 45 at p. 49, *Environmental Chemicals and Breast Cancer Risk* (2002) ("Animal studies...are important to help predict cancer risk when human studies are unavailable.")

When animal studies are offered to demonstrate causation in a tort case, experts also provide additional information to justify the extrapolation to humans. *Ref. Manual* at 409. Expert opinions based on animal data have been excluded where the expert did not review similarities and differences between humans and the animal species in which the compound was tested. *E.g., Gen. Elec. Co. v. Joiner*, *supra*, at 144 (district court did not abuse its discretion in ruling inadmissible expert testimony based on "seemingly far-removed" animal studies where party failed to explain why the extrapolation was scientifically proper); *Domingo v. T.K.*, 289 F.3d 600, 606-607 (9th Cir. 2002) (finding that district court's exclusion of expert's causation testimony was not an abuse of discretion, in part because expert did not provide "analytical support" for his extrapolation of animal study results to humans and also because there was no evidence that the expert had applied a valid scientific method in developing his theory and there were unexplained gaps between the expert's premises and his conclusion); *Turpin*

v. Merrell Dow Pharms., Inc., 959 F.2d 1349, 1360 (6th Cir. 1992) (holding that expert's testimony was inadmissible where the record failed to make clear why the effects of Bendectin in rats and rabbits could be extrapolated to humans); *Hall v. Baxter Healthcare Corp.*, 947 F.Supp. 1387, 1410 (D.Or. 1996) ("Extrapolations of animal studies to human beings are generally not considered reliable in the absence of a scientific explanation of why such extrapolation is warranted."). Animal studies are not generally admissible where contrary epidemiological evidence in humans exists. *See Richardson v. Richardson-Merrell, Inc.*, 857 F.2d 823, 830 (D.C. Cir. 1988), *cert. denied*, 493 U.S. 882 (1989) (finding that animal studies of effects of Bendectin could not establish general causation of birth defects in humans where there was an "overwhelming" amount of contrary epidemiological evidence).

There are two significant disadvantages in relying on animal studies. First, when extrapolating from animals to humans, differences in absorption, metabolism, and other factors may confound results. Second, toxicological expert opinions are "almost always" based on animal studies that involve doses of a suspected carcinogen that are significantly higher than animal doses comparable to expected human exposure. This is often necessary to obtain statistically significant predictions of the effects of realistic doses. *Ref. Manual* at 409.[4]

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[4] The *Ref. Manual* explains why this is so. Suppose the background rate of cancer in, say, rats not exposed to the suspected carcinogen is 6 in 100. And suppose the *suspected* rate of cancer for rats at a humanly realistic dose of the carcinogen exposed to is 1 in 100. That means that using the comparable human dose, even an experiment involving a total of 200 rats (100 exposed rats and 100 controls) would be expected to reveal cancer in 6 control rats and in 7 exposed rats. This difference would not be statistically significant. However, if an investigator administered ten times the realistic dose and discovered that 16 out of 100 of the exposed rats contracted cancer (compared with only 6 out of 100 rats in the unexposed controls), the measured effect of the carcinogen would be statistically significant. Instead of seven cancer ridden rats (6 plus 1 attributable

(continued...)

Extrapolation from high-dose animal studies, however, assumes a predictable relationship between dose and the probability that an exposed animal will be diagnosed with cancer. *Ref. Manual* at 345-46, 409, 414.

2. Differential Diagnosis

Differential diagnosis, the process of elimination that physicians routinely use to identify the most likely cause of a particular individual's illness, is an acceptable source of data on specific causation. *Hall, supra*, at 1413. By examining the patient's symptoms, medical history, diagnostic test results, etc., a doctor can eliminate alternative causes and reach a conclusion about the most likely cause of a particular patient's condition. "[T]o the extent that a doctor utilizes standard diagnostic techniques in gathering this information, the more likely [it is that a court will] find that the doctor's methodology is reliable." *In re Paoli, supra*, at 759. It is important to note, however, that differential diagnosis cannot demonstrate general causation, because it assumes, without proving, that all of the potential causes considered are capable of causing the condition at issue. "Indeed differential diagnosis *assumes* that general causation has been proven for the list of possible causes it eliminates[.]" *Hall, supra*, at 1413.

3. Epidemiological studies

The field of epidemiology addresses the incidence, distribution and etiology (causation) of disease in human populations, *Ref. Manual* at 335, by comparing individuals exposed to a particular agent to unexposed individuals to determine whether exposure increases the risk of disease. *Hall, supra*, at 1403. A common approach to expressing the association between exposure to an agent

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[4](...continued)
to the suspected rate), there are 6 plus 10 attributable to the doses administered. Assuming a predictable dose-response relationship, a tenfold increase in dose results in a tenfold increase in the number of rats diagnosed with cancer. From this, the investigator could conclude that a realistic dose results in a rate of cancer of 1 in 100 in rats. *Ref. Manual* at 409.

and disease in a population is the agent's "relative risk." The relative risk is obtained by dividing the proportion of individuals in the exposed group who contract the disease by the proportion of individuals who contract the disease in the non-exposed group. For example, if a study found that 10 out of 1000 women with breast implants were diagnosed with breast cancer and 5 out of 1000 women without implants (the "control" group) were diagnosed with breast cancer, the relative risk of implants is 2.0, or twice as great as the risk of breast cancer without implants.[5] This is so, because the proportion of women in the implant group with breast cancer is 0.1 (10/1000) and the proportion of women in the non-implant group with breast cancer is 0.05 (5/1000)). And 0.1 divided by 0.05 is 2.0.

"When [epidemiological] studies are available and relevant, and particularly when they are numerous and span a significant period of time, they assume a very important role in determinations of questions of causation." *Richardson v. Richardson-Merrell, Inc.*, *supra*. *See also Ref. Manual* at 335 n.2 ("Epidemiologic studies have been well received by courts trying mass tort suits. Well-conducted studies are uniformly admitted.") (citation omitted). Because epidemiology is concerned with the incidence of disease in populations, epidemiology is probative of general causation; "specific causation is beyond the domain of the science of epidemiology." *Ref. Manual* at 381. However, and as described in the next sub-section, the Ninth Circuit has held that an epidemiological study is admissible to prove specific causation under

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[5] A relative risk of 1.0 would suggest that implants have no effect on the incidence of cancer and that a relative risk between 0 and 1.0 could indicate a protective effect. In the above example, a relative risk of 1.0 would correspond with a finding that 5 out of 1000 women with implants contracted breast cancer – the same number as in the control group. A relative risk smaller than 1.0 would correspond with a finding that fewer than 5 out of 1000 women with implants were found to have breast cancer.

California tort law if the study shows that the relative risk is greater than 2.0.

C. Usefulness

To be admissible, proffered expert testimony must assist the average trier of fact. Fed. R. Evid. 702. The Supreme Court characterizes this prong as "the 'fit' between the testimony and an issue in the case." *Daubert II*, *supra*, at 1320 (citing *Daubert I*, at 591). Testimony "fits" a case if it "logically advances a material aspect of the proposing party's case." *Id.* at 1315.

Certain relative risk thresholds are required for the statistical results of an epidemiological study to "assist the trier of fact" in assessing causation. *Daubert II*, at 1320. Defendants argue at several points in their papers that to prove general causation, Plaintiff must establish that the relative risk of contracting breast cancer from PUF-coated implants is at least 2.0. *E.g.,* Lappé Reply at 8. That argument is based on a misunderstanding of relative risk, a mis-reading of Ninth Circuit precedent and a lapse in basic logical reasoning. As explained below, this "doubling of the risk" requirement applies to statistical evidence proffered to prove *specific*, not *general* causation.

As explained in Section III.B.3, *supra*, the relative risk is a statistical term derived from a study of hundreds or thousands of subjects. It is obtained by dividing the proportion of individuals in an exposed group who contract the disease by the proportion of individuals who contract the disease in a non-exposed group. Thus, any properly-performed epidemiological study that finds a relative risk greater than 1.0 signifies that exposure to an agent increases the probability of contracting the disease. Where the study properly accounts for potential confounding factors and concludes that exposure to the agent is what increases the probability of contracting the disease, the study has demonstrated *general* causation – that exposure to the agent "is capable of causing [the illness at issue] in the general population." *In re Hanford*, *supra*, at 1134. A relative risk of 2.0, sometimes referred in certain contexts as a "doubling dose," is not

necessary to establish generic causation). *Id.* at 1137.

When statistical analyses or probabilistic results of epidemiological studies are offered to prove *specific* causation, however, under California law those analyses must show a relative risk greater than 2.0 to be "useful" to the jury. *Daubert II, supra*, at 1320. This is so, because a relative risk greater than 2.0 is needed to extrapolate from generic population-based studies to conclusions about what caused a specific person's disease. When the relative risk is 2.0, the alleged cause is responsible for an equal number of cases of the disease as all other background causes present in the control group. Thus, a relative risk of 2.0 implies a 50% probability that the agent at issue was responsible for a particular individual's disease. This means that a relative risk that is greater than 2.0 permits the conclusion that the agent was more likely than not responsible for a particular individual's disease. *Ref. Manual* at 384, n.140 (citing *Daubert II*).

Thus, suppose a study finds that 100 out of a group of 100,000 women with breast implants developed breast cancer. If, as a result of a different study comparing rates of cancer in women with implants to women without implants, a risk factor of 2.0 was known to be associated with breast implants, this would mean that the cancers in 50 of those 100 cancerous women were caused by implants. Since the study alone provides no way of knowing *which* of the 100 women with breast cancer are in the group of 50 whose cancer was caused by implants, the probability that any one of those women's cancer was caused by her implants would be only 50% - - just short of "more likely than not." However, a risk factor that is greater than 2.0 would mean that the cancers of more than 50 of the 100 women were caused by breast implants, making it more likely than not that breast implants were the cause of any one of those women's cancer. This is the reasoning underlying the "doubling of the risk" requirement of *Daubert II*.

Proof of general causation is a prerequisite to applying this statistical "doubling risk" approach to specific causation. *Ref. Manual* at 383-84.

Additionally, this approach to proving specific causation assumes that the plaintiff is comparable to the subjects of the epidemiological study and that there were no other causal agents present in the plaintiff's case not accounted for by the study. *Id.* at 385. Depending on the differences between the plaintiff and the subjects of the study, this can weigh in favor or against specific causation. For example, here Plaintiff argues that because Cagle became pregnant shortly after receiving her implants, the release of hormones associated with her pregnancy made her breast cells more susceptible to potential mutation by TDA, thus making her different from the groups evaluated in the epidemiological studies.

The foregoing discussion demonstrates the inherent difficulties associated with use of statistical data to prove specific causation. As the Ninth Circuit has observed,

> No doubt, there will be unjust results under this substantive standard. If a drug increases the likelihood of [harm], but doesn't more than double it, some plaintiffs whose injuries are attributable to the drug will be unable to recover. There is a converse unfairness under a regime that allows recovery to everyone that *may* have been affected by the drug. . . . One can conclude from this that unfairness is inevitable when our tools for detecting causation are imperfect and we must rely on probabilities rather than more direct proof.

Daubert II, *supra*, at 1320, n.13.

IV. Dr. Richard Neugebauer (epidemiologist)

The crux of Dr. Neugebauer's testimony seeks to explain why in his view the existing epidemiological studies of PUF breast implants and cancer rates are either unreliable or not relevant to this case. At his deposition, Dr. Neugebauer agreed that a "fair summary of his bottom line opinion" is that "epidemiologic evidence from which to rule out a relationship between (PUF) implants and breast cancer is lacking." Dunleavy Decl. Exh. C at 36-37. He also states that "the one study to examine this question in a rigorous manner reported at least a doubling of breast cancer risk . . . ." *See* Neugebauer Opp. Exh. B ("Neugebauer Expert

Report").

A. Proposed Testimony

Neugebauer intends to testify to the following:

The epidemiological studies concluding that there is no association between breast implants and cancer are either unreliable or inapplicable to this case

Support

- Defendants rely on studies which failed to eliminate confounding factors. Those studies also failed to address that women who select breast augmentation are not a random sample of the female population. Neugebauer Expert Report at 2-3.
- Defendants rely on studies which did not have a sufficient number of subjects. Given the relative infrequency of individual cancers, "truly enormous" study sizes are needed. *Id*. at 3.
- Defendants rely on studies for which response rates (*i.e.* the proportion of persons solicited who responded to study questionnaires) fell below 70%, a rate considered "borderline acceptable." High non-response rates may suggest participants and non-participants differ on basic sociodemographic characteristics. *Id*. at 3.
- Defendants rely on studies which employed self-report questionnaires rather than objective validation or clarification by independent researchers. *Id*. at 4.
- Many of the epidemiological studies of breast implants are totally unhelpful, because they fail to identify which type of implants were used in each subject. This is significant, because PUF-covered implants comprise a relatively small proportion of all implants). *Id.* at 4-5.

One epidemiological study provides "suggestive evidence" that there is an association between breast implants and breast cancer.

Support

- A study that monitored cancer rates by implant type found that women with PUF implants experienced a doubling of their cancer risk. *Id.* (citing Brinton *et al.*, *Breast Cancer Following Augmentation Mammoplasty*, 11 Cancer Causes and Control 819 (2000) (Neugebauer MIL Exh. 7)); Neugebauer MIL Exh. 1 (Neugebauer Depo.) at 36:3-37:3.

B. Qualifications

Defendants argue that Neugebauer is not qualified to testify about epidemiological studies, because he "is not a medical doctor" and "has never conducted an epidemiologic study examining the relationship between breast implants and cancer." Neugebauer MIL at 2. They also point out that Neugebauer has merely "review[ed] certain articles" and that "Neugebauer never took any interest in the alleged health effects of breast implants until after he was contacted to serve as a paid expert witness." *Id*. at 3.

Defendants' argument is meritless. Neugebauer is a general epidemiologist, with extensive experience in designing, conducting and analyzing epidemiological studies as well as teaching others how to design, conduct, and analyze such studies. Neugebauer's credentials are specific to an inquiry about the methodological soundness of Defendants' epidemiological data. Furthermore, Neugebauer has testified that "the methods of epidemiology are fundamentally the same whether the possible risk factor is [PUF], asbestos, or serum cholesterol levels. The available study designs are also the same whether the outcome is breast cancer, lung cancer, or coronary heart disease." Neugebauer Opp. Exh. E (Neugebauer Decl.) at 2. That Neugebauer specializes in perinatal and psychiatric epidemiology should not preclude him from offering an opinion regarding cancer epidemiology.

Given these facts and the liberal construction of expert qualifications FRE 702 requires, Neugebauer is certainly qualified to evaluate and explain the available epidemiological evidence concerning breast implants.

C. Reliability

As mentioned previously, Neugebauer intends to provide the following testimony: (1) Defendants' epidemiological studies are methodologically flawed and do not specifically address whether PUF-covered breast implants are carcinogenic and (2) there is "suggestive [epidemiological] evidence" that PUF-

covered breast implants *are* carcinogenic. Neugebauer MIL Exh. 1 (Neugebauer's Depo.) at 36:3-37:3.

1. Methodological flaws

Neugebauer's analysis of the existing epidemiological evidence is admissible. Meta-analyses that probe the methodological validity of medical studies are not unprincipled or unscientific. Neugebauer's testimony is based upon well known statistical principles – that the size of the study makes a difference, that the ability to control for certain variables is essential and that response rates and data collection methods affect results. Neugebauer has evaluated the available studies and has concluded that, given what he perceives as design flaws, those studies do not support Defendants' contention that implants do not cause breast cancer.

The various *Daubert* factors also support a finding that Neugebauer's criticisms of the available studies are admissible. The statistical underpinnings of epidemiology are well-tested. They have been subjected to peer review and publication. They are generally accepted in the scientific community. Furthermore, Neugebauer did not develop the techniques he employs to evaluate Defendants' studies for the purposes of litigation, nor has he extrapolated from an accepted premise to an unfounded conclusion.

Moreover, Neugebauer's (correct) assessment that the available epidemiological studies do not reach even tentative conclusions about whether *PUF-coated implants* (as opposed to implants generally) are carcinogenic, is also reliable and hence admissible. In their summary judgment Motion, Defendants cite many studies that they contend support their argument that there is no association between PUF-coated implants and breast cancer. SJ Mot. Exhs. 15-33.[6] However, those studies determined that the *silicone* in breast implants are

[6] The studies Defendants provided are: Deapen *et al.*, *The Relationship* (continued...)

[6](...continued)
Between Breast Cancer and Augmentation Mammaplasty: An Epidemiologic Study, 77 Plastic & Reconstructive Surg. 361-67 (1986) (SJ Mot. Exh. 15); Deapen *et al.*, *Augmentation Mammaplasty and Breast Cancer: A 5-Year Update of the Los Angeles Study*, 89 Plastic & Reconstructive Surg. 660-65 (1992) (*id.*); Deapen *et al.*, *Are Breast Implants Carcinogenic? A 14 Year Follow-Up of the Los Angeles Study*, 99 Plastic & Reconstructive Surg. 1346-53 (1997) (*id.*); Brinton *et al.*, *Breast Enlargement and Reduction: Results from a Breast Cancer Case-Control Study*, 97 Plastic & Reconstructive surg., 269-75 (1996) (*id.* Exh. 16); Frus *et al.*, *Breast Implants and Cancer Risk in Denmark*, 71 Int'l J. Cancer 956-58 (1997) (*id.* Exh. 17); McLaughlin *et al.*, *Cancer Risk Among Women with Cosmetic Breast Implants: A Population-Based Cohort Study in Sweden*, 90 J. Nat'l Cancer Inst. 156-58 (1998) (*id.* Exh. 19) & 86 J. Nat'l Cancer Inst. 1424 (1994) (*id.* Exh. 18); Berkel *et al.*, *Breast Augmentation: A Risk Factor for Breast Cancer?* 326 New England J. of Medicine 649-53 (1992) (*id.* Exh. 20); Petit *et al.*, *Can Breast Reconstruction with Gel-Filled Silicone Implants Increase the Risk of Death and Second Primary Cancer in Patients Treated by Mastectomy for Breast Cancer?* 94 Plastic & Reconstructive Surg. 115-19 (1994) (*id.* Exh. 21); Kern *et al.*, *Carcinogenic Potential of Silicone Breast Implants: A Connecticut Statewide Study*, 100 Plastic & Reconstructive Surg. 737-47 (1997) (*id.* Exh. 22); Gabriel *et al.*, *Risk of Connective-Tissue Diseases and Other Disorders After Breast Implantation*, 330 New England J. of Medicine, 1697-1702 (1994) (*id.* Exh. 23); Engel *et al.*, *Human Breast Sarcoma and Human Breast Implantation: A Time Trend Analysis Based on SEER Data (1973-1990)*, 48 J. Epidemiol. 539-44 (1995) (*id.* Exh. 24) & 89 Plastic & Reconstructive Surg. 571-72 (1992) (*id.* Exh. 25); Malone *et al.*, *Implants and Breast Cancer*, 339 The Lancet 1365 (1992) (*id.* Exh. 26); Duffy *et al.*, *Health Risks of Failed Silicone Gel Breast Implants: A 30-Year Clinical Experience*, 94 Plastic & Reconstructive Surg. 295-99 (1994) (*id.* Exh. 27); Park *et al.*, *Silicone Breast Implants and Breast Cancer*, 7 The Breast 22-26 (1998); Petit *et al.*, *Does Long-Term Exposure to Gel-Filled Silicone Implants Increase the Risk of Relapse After Breast Cancer?* 84 Tumori 525-28 (1998) (*id.* Exh. 29); Brinton *et al.*, *Breast Cancer Following Augmentation Mammoplasty (United States)*, 11 Cancer Causes & Control 819-27 (2000) (*id.* Exh. 30 & Neugebauer MIL Exh. 7); Skinner *et al.*, *Breast Cancer After Augmentation Mammoplasty*, 8 Annals of Surgical Oncology 138-44 (2001) (SJ Mot. Exh. 31).

Although a few of the above studies included observations about small numbers of women with PUF-coated implants, none of them purported to reach any statistically sound conclusion about whether PUF-coated implants cause

(continued...)

not associated with cancer. Not one of those studies purported to reach any conclusion about the rate of breast cancer in women receiving PUF-coated implants. Many of the studies did not report the number of subjects that had received PUF-coated implants and in those that did, it is clear that the number of PUF subjects was a tiny fraction of the total number of subjects studied. For example, in the 1997 study by Deapen *et al.* only 69 out of the 3182 subjects had received PUF-coated implants. *Id.* Exh. 15 at 1348; Neugebauer MIL Exh. 6 at 114. The study reported that one patient with polyurethane sponge implants developed breast cancer, but did not purport to reach any conclusion about PUF-coated implants generally. SJ Mot. Exh. 15 at 1351; Neugebauer MIL at 117. Similarly, the 1996 Brinton study that Defendants proffered concluded that "[f]urther studies are needed on risks associated with . . . [PUF]-coated implants." SJ Mot. Exh. 16 at 274.

Defendants appear to argue that a study published by Brinton in 2000 reached a conclusion about the risk of cancer from PUF-coated implants. Neugebauer MIL at 12-13. That study did no such thing. The study's focus was the risk of breast cancer from breast implants in general and only 1.3% of the implants in the 13,488 patients studied were PUF-coated. *Id.* Exh. 7 at 121, 125. Based on the very limited sample of individuals with PUF-coated implants, Brinton found that the relative risk of PUF-covered implants was 1.99 with a margin of error between 0.5 and 8.0 at the 95% confidence level.[7] *Id.* at 125.

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[6](...continued)
breast cancer.

[7] The study actually reported its results in terms of a "standardized incidence ratio" ("SIR"), which is computed by taking the number of observed incidences of breast cancer in study participants with breast implants, divided by the "expected" number of incidences of breast cancer in a hypothetical cohort of women with similar characteristics who do not have implants. Neugebauer MIL (continued...)

That means that 95 times out of 100 a study of that type would yield a relative risk value somewhere between 0.5 and 8.0. This huge margin of error associated with the PUF-specific data (ranging from a potential finding that implants make a woman 50% *less likely* to develop breast cancer to a potential finding that they make her 800% *more likely* to develop breast cancer) render those findings meaningless for purposes of proving or disproving general causation in a court of law.

Plaintiff does not dispute that the National Academy of Sciences Institute of Medicine Committee on the Safety of Silicone Breast Implants commented as follows on PUF implants:

> Given the relatively small number of women with polyurethane implants still in place, the natural breast cancer incidence in women and the lack of evidence for polyurethane carcinogenesis, which implies at most a small effect, if any, of polyurethane in causing human cancer, it is unlikely that any study of patients with existing implants will be able to provide sufficient evidence of an association between these implants and cancer. At present, evidence is lacking to conclude that there is an association between polyurethane-coated implants and cancer, and the way that [sic] existing evidence suggests that there is no such association. Since the implantation of polyurethane-coated breast implants within the United States is unlikely, these conflicting studies may never be reconciled.

Item 7 on Revised Statement of Uncontroverted Facts and Conclusions of Law.

The absence of meaningful epidemiological data on PUF-covered implants

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[7](...continued)
Exh. 7 at 123. (The term "cohort" means "any designated group of persons followed or traced over a period of time to examine health or mortality experience." *Ref. Manual* p.389.) This is equivalent to the "relative risk" described in Section III.B.1.3.

is not surprising, given that manufacturers of PUF-covered implants suspended shipments in May 1991 and only ten percent of women with implants had the PUF-coated type at that time. Lappé Expert Report at 8; Kern *et al.*, *Carcinogenic Potential of Silicone Breast Implants: A Connecticut Statewide Study*, 100 Plastic & Reconstructive Surg. 737 (1997) (SJ Mot. Exh. 22).

2. "Suggestive" Evidence

Neugebauer's assertion that the 2000 Brinton study contains "suggestive" evidence of an association between PUF-coated implants and cancer is not reliable. As discussed above, only 1.3% of the implants in that study were PUF-coated, a sample size so small that the risk factor could be anywhere between 0.5 and 8.0 ninety-five percent of the time. The Brinton study never reached any conclusion about PUF-coated implants specifically and, given the very large margin of error, any causation opinion based on the PUF-specific results of that study would be unreliable. Indeed, when asked to clarify what he meant by "suggestive" evidence, Neugebauer testified that he meant that "more work has to be done to rule it in or out." Neugebauer MIL Exh. 1 (Neugebauer Depo.) at 38:13-16. This does not satisfy the preponderance of the evidence causation standard.

Additionally, Neugebauer's proposed testimony about the Brinton study is unreliable, because it ignores the rigorous standards and methodology Neugebauer himself applies to the other studies. "[A]ny step that renders [the expert's] analysis unreliable . . . renders the expert's testimony inadmissible. This is true whether the step completely changes a reliable methodology or merely misapplies that methodology." Fed. R. Evid. 702 Advisory Committee's Notes 2000 (quoting *In re Paoli*, *supra*, at 745 (emphasis omitted)). Neugebauer ignores that the PUF-specific findings of the Brinton study suffer from the same flaws he points to in the other studies: (a) the sample size of subjects with PUF implants was vanishingly small; (b) the overall response rate (approximately

71%, Neugebauer MIL at 122) was only "borderline acceptable," Neugebauer Expert Report at 3; and (c) the study relied on questionnaires rather than objective validation or clarification. Neugebauer MIL Exh. 7 at 122; Neugebauer Expert Report at 4.

D. Usefulness

Defendants argue that Neugebauer's testimony criticizing the available epidemiological studies about breast implants and opining that "more work has to be done" to ascertain whether PUF-coated implants cause cancer is not useful to the jury. Defendants appear to be arguing that because the testimony does not show that breast implants cause breast cancer, Neugebauer's opinion does not advance Plaintiff's case and is thus irrelevant. This argument lacks merit.

It is clear from Defendants' papers that they intend to proffer at least fifteen epidemiological studies concluding that there is no evidence that silicone breast implants cause cancer. Plaintiff is entitled to use Neugebauer, an expert in epidemiology, to point out the main problem with those studies – that they reach no conclusion about the propensity of *PUF-coated* implants to cause cancer. This is classic rebuttal expert testimony. Aside from his testimony about "suggestive evidence" (which will be excluded), Neugebauer's purpose is to explain why the studies Defendants intend to proffer are inapposite. Plaintiff is entitled to inform the jury that Defendants' studies about silicone implants did not reach conclusions about the carcinogenicity of PUF-coated implants and about those studies' purported methodological limitations.[8]

Defendants' reliance on *Kelley v. Am. Heyer-Schulte Corp., et al.*, 957 F.Supp 873 (W.D. Tex. 1997) and *Hall*, *supra*, is unfounded. In *Kelley*, the

[8] Plaintiff's motion *in limine* to exclude "cumulative and irrelevant" expert testimony essentially argues that these studies ought to be excluded, because they are irrelevant and prejudicial. If the Court were to exclude those studies altogether, then Neugebauer's testimony probably would be irrelevant.

plaintiff's epidemiology expert had testified that the available studies provided limited evidence of an association between breast implants and Sjogren's Syndrome (the injury at issue in that case) and that "more studies are needed." *Kelley*, 957 F.Supp. at 881. At the same time, however, the expert also intended to rely on those inconclusive studies to assert that a causal relationship did exist between breast implants and Sjogren's Syndrome. Unlike in *Kelley*, Plaintiff does not intend to rely on the same studies Neugebauer distinguishes to advance a positive theory of causation. In *Hall*, the court excluded an expert's "reanalysis" of existing epidemiological studies because it was unreliable and the witness's criticisms of the studies were not accepted within the scientific community. The Court also noted that it had already determined that the studies in question were inadmissible, thus rendering the expert's testimony about them irrelevant. *Id.* at 1406-07.

E. Conclusion

For the foregoing reasons, Neugebauer's testimony regarding the reliability and applicability of Defendants' studies is admissible under Fed. R. Evid. 702.

Neugebauer's claim that the 2000 Brinton study offers "suggestive evidence" of the carcinogencity of PUF-coated implants is not admissible. That study did not make any finding about whether PUF-coated implants are carcinogenic and the error rate associated with the PUF-specific data makes it wholly unreliable. Additionally, Neugebauer's conclusions regarding the Brinton study are vulnerable to the same criticisms he levies against Defendants' studies, namely, that the sample sizes were too small and the response rates were too low.

V. Dr. Christopher Batich (polymer chemist)

A. Proposed Testimony

Batich intends to testify to the following.

PUF-coated implants degrade after implantation in humans, releasing TDA

Support

- 1991 and 1995 research findings that PUF-covered breast implant patients who had previously tested negative for TDA in their blood and urine tested positive post-implantation. Chan *et al.*, *Detection of toluenediamines in the urine of a patient with polyurethane-covered breast implants*, 37 Clinical Chemistry, 756-58 (1991) (Batich Opp. Exh. W); Sepai, *et al.*, *Exposure to toluenediamines from polyurethane-covered breast implants*, 77 Toxicology Letters 371-78 (1995) (Batich Opp. Exh. T).[9]

- A 1993 *in vitro* study demonstrating that MemePUF-covered implants contained "significant amounts" of residual TDA while degrading at 0.8% per year. Benoit *et al.*, *Degradation of polyurethane foams used in Meme breast implant*, 27 J. of Biomedical Material Research, 1341-48 (1993) (Batich Opp. Exh. P)). *See also* Luu, *et al.*, *Characterization of Polyesterurethane Degradation Products*, 5 J. of Applied Biomaterials, 1-7 (1994) (Batich Opp. Exh. R)

- Summarizing the available research, the National Toxicology Program ("NTP") stated in 2001 and in December 2002 that TDA is a degradation product of the PUF used in Meme silicone breast implants. The NTP reported that elevated levels of TDA (between 0.4 to 6 ng/ml) were detected in the urine and plasma of patients up to two years after implantation. SJ Opp. Exh. 54 at 850 (Ninth Report); http://ehp.niehs.nih.gov/roc/toc10.html (Tenth Report).[10]

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[9] *See also* Sinclair *et al.*, *Biodegradation of the Polyurethane Foam Covering of Breast Implants*, 92 Plastic & Reconstructive Surg. 1003-1013 (1993) (Batich Opp. Exh. O) (chemical analysis of polyurethane coating of implants extracted from patients after several years of use concluded that polyurethane foam covering degrades *in vivo*).

[10] Defendants have proffered a 1997study conducted by Jane Gale of the Pharmaceutical Research Institute of Defendant Bristol-Myers Squibb concluding that the PUF-coating degrades at such a negligible level that it creates only a one in one million risk of cancer. Hester, *et al.*, *Measurement of 2,4-Toluenediamine in Urine and Serum Samples from Women with Même or Replicon Breast Implants*, 100 Plastic & Reconstructive Surg. 1291-98 (1997) (SJ Mot. Exh. 35 at (continued...)

- Defendants' expert Dr. Gale has testified that she has "no reason . . . to controvert the basic scientific premise that TDI-based foam [PUF] will degrade and release TDA." Batich Opp. Exh. BB at 362:5-10 (Cross-examination of Dr. Gale in *Brusca* litigation).

- Batich conducted his own 1989 study intended to characterize the degradation products of the polyurethane used in PUF-coated implants. He identified the chemical reaction that causes PUF to degrade and release TDA. Although the conditions used in the experiment (150 C and concentrated sodium hydroxide) were quite different from *in vivo* conditions, Batich maintains that the harsh conditions merely accelerated the same chemical reaction as would occur *in vivo*. The purpose of the experiment, Batich says, was not to assess how much TDA will be released under physiologic conditions, but to figure out what the hydrolysis products of PUF are. Batich *et al.*, *Toxic Hydrolysis Product From a Biodegradable Foam Implant*, 23 J. Biomed. Mater. Res.: Applied Biomaterials, 311-19 (1989) (Batich Opp. Exh. F); Batich*, et al.*, *Letter to the Editor and Response*, 1 J. Applied Biomaterials 193-95 (1990) (Batich Opp. Exhs. G & H).

As to Cagle, in her Meme implant a polyester based polyurethane foam was used rather than the more stable oliphatic or polyether based one. This led to more rapid degradation.

Defendants never conducted studies before placing PUF-coated implants on the market to determine the biodegradation products of those implants. Because such studies were "simple to carry out and inexpensive[,] [t]here was no good reason not to have done them, and the failure to test . . . was unreasonable and unsafe." Batich Opp. Exh. B ("Batich Expert Report") at 12.

Support

- Batich says that before marketing a biomaterial, studies ought to be conducted to determine (a) what degradation products are formed; (b) what quantity of them are released; (c) the biological properties of the released components; (d) where the products travel within the body and (e) what biological changes they cause. *Id.*

B. Qualifications

1. Biodegradation of PUF-Coated Implants

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[10](...continued)
1291). The mere existence of contrary studies is not a sufficient basis to exclude expert testimony.

Defendants argue that Dr. Batich is not qualified to opine about whether TDA released from PUF-coated implants can cause breast cancer. Plaintiff responds that Batich is not a "causation" witness, but "is offered as an expert . . . on the issue of the defective design of defendant's Meme implant." Batich Opp. at 1. According to Plaintiff, the purpose of Batich's testimony is to support Plaintiff's negligence claim (*see* Am. Compl. ¶¶ 95-104) by testifying that Defendants breached a duty of care when they failed to conduct degradation studies on the polyurethane foam and when they failed to use a more stable oliphatic or polyether-based foam. *Id.*; Batich Expert Report. Defendants respond that Batich really *is* a causation witness, because his duty-of-care opinion is "wholly based on his opinion that polyurethane breast implants or their breakdown products *cause* cancer." Batich Reply at 2.

Both parties are partly correct. Batich's testimony *is* an essential part of Plaintiff's causation theory, but in a much more limited way than Defendants represent. Defendants are correct that Dr. Batich is not qualified to testify that TDA is a probable human carcinogen or that TDA that may have been released from Toni Cagle's implants caused her breast cancer, but nothing in Batich's expert report indicates that he intends to so testify anyway. Batich Expert Report. However, Batich, a polymer chemist who directs a biomedical engineering program at the University of Florida, *is* qualified to testify about the mechanisms of hydrolysis of PUF and the *in vitro* and human studies finding that PUF degrades to TDA. Although Batich is not a physician or biochemist, he may opine about these studies because they primarily involve chemical analyses of patients' blood and urine using classic tools of the analytical chemistry trade, such as gas chromatography and mass spectrometry. *E.g. Sepai et al.* (Batich Opp. Exh. T) at 371-72. A physician isn't needed to interpret a study merely because the analysis involves a urine sample.

2. Duty of Care

Defendants argue that Batich's duty-of-care testimony is inadmissible because it relies on the premise that PUF implants cause cancer. Not so. First, Batich's testimony is *not* based on that premise; he intends to testify that Defendants breached their duty of care by marketing PUF implants without carrying out what he characterizes as simple and inexpensive tests to determine whether the polyurethane would break down *in vivo*. He also intends to testify that Defendants should have used a more stable polyether-based foam than the polyester-based one they actually used. While it is true that Plaintiff cannot prevail on his negligence claim unless he shows causation, Batich's testimony – essentially that Defendants breached a duty of care by not taking reasonable precautions – does not require a prior finding of causation. Second, to the extent that Batich may refer to the TDA breakdown product of PUF as a known animal carcinogen, he may permissibly rely on the testimony of Dr. Lappé (see *infra* Section VI) as support.

Defendants also argue that Batich's duty-of-care testimony is inadmissible, because Batich is not qualified to testify about medical device testing standards. Batich MIL at 16. More specifically, they argue that Batich's five-pronged pre-market testing requirement (see Section V.A., *supra*) is inadmissible, because it merely constitutes "what [Batich] think[s] would be good prudent practice for someone who is producing a medical device." Batich MIL Exh. 1 ("Batich Depo.") at 62:6-23.

Defendants are correct that Batich is not qualified to opine that Defendants breached a duty of care by failing to conduct certain tests. As a basis for Batich's expertise, Plaintiff notes that Batich worked in the quality control department of a pharmaceutical company[11] between 1965 and 1967, that he published several

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[11] Batich's *curriculum vitae* calls White Laboratories a pharmaceutical company (Batich Opp. Exh. A at 1); Plaintiff refers to it as a medical device (continued...)

papers about medical devices and biomaterials, and that he holds several patents on medical devices. Batich Opp. at 6. This is insufficient to qualify Batich as an expert on when and whether it is "unreasonable" not to conduct biodegradation tests on a biomaterial before using it in an implantable medical device. Plaintiff proffers no evidence that Batich has any experience developing an implantable medical device for general use or that he has any foundational knowledge about what standard practices exist in the industry in this regard. Batich has testified that other than his studies of the hydrolysis products of PUF and "gel bleed" from implants, he has not tested any other medical device for biodegradation products. Batich Depo. at 65:18-67:2.

Batich *is* qualified, however, to describe how one could test the PUF-coating to determine whether it releases toxic products. He is also qualified to testify about the amount of time it would take to conduct those tests and how much it would cost. Defendants nonetheless argue that even this limited testimony would be inadmissible, because Batich is not familiar with the applicable FDA regulatory standards. That argument lacks merit. What the FDA requires a medical device manufacturer to do is not the *per se* standard for determining what that manufacturer's duty is in a state law negligence case. *See Goodlin v. Medtronic, Inc.*, 167 F.3d 1367, 1382 (11th Cir. 1999) (FDA's pre-market approval of medical device did not preempt state law tort claim); *Hill v. Searle Labs*, 884 F.2d 1064, 1068 (8th Cir.1989) ("FDA approval is not a shield to liability. . . . FDA regulations are generally minimal standards of conduct unless Congress intended to preempt common law, which Congress has not done in this area."). Although Batich cannot say whether the FDA requires manufacturers to test for biodegradation products of new biomaterials, this is not fatal to his expert testimony.

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[11](...continued)
manufacturer. Batich Opp. at 6.

C. Reliability and Usefulness

Dr. Batich's testimony is both reliable and relevant. His testimony regarding the *in vivo* breakdown products of PUF is based on his own published, peer-reviewed study and other published, peer-reviewed studies. *See supra* Section V.A. That Defendants can point to contrary studies is not sufficient to render Batich's testimony inadmissible. In addition, Batich's testimony is relevant, because the breakdown of PUF is an essential aspect of Cagle's causation theory.

Batich may not testify, however, about his 1989 study findings on the amount of TDA released from PU foam. That study employed extreme experimental conditions. He placed a 500 milligram sample of PUF in concentrated sodium hydroxide overnight at a temperature of 150 C to determine what the hydrolysis products of PUF were. He determined that in those conditions about 85 milligrams of TDA (17 percent of the sample) was released. Batich Opp. Exh. F at 52. Since there is no evidence that PUF degrades at such a fast rate *in vivo*, Batich lacks foundation to testify about how much TDA was produced in his study and it would be prejudicial for him to do so.

D. Conclusion

Dr. Batich's testimony that the polyurethane coating of PUF-coated implants hydrolyzes *in vivo* to produce TDA is admissible. He may discuss the available literature on the subject, including the amounts of TDA found by researchers in the blood and urine of patients shortly after those patients received PUF-coated implants. However, because he carried out his own 1989 *in vitro* study under extreme conditions, his own findings regarding the amount of TDA released would not be reliable or relevant and may be prejudicial. Batich also may testify about how one would test for biodegradation products of a biomaterial, how long such a test may take and how much it would cost. He may not testify that "wide use" of all biomaterials must be preceded by such tests or

that any failure to test the product(s) used in this case was "unreasonable." (Ultimately, of course, the question of whether Defendants breached a duty of care by not testing the PUF coating or when they chose to use a polyester based polyurethane instead of a more stable plastic would be an issue for the jury.)

VI. Dr. Marc Lappé (toxicologist)

A. Proposed Testimony

Lappé intends to testify to the following:

Studies have shown that polyurethanes, when implanted in rats, are carcinogenic.

Support

- A 1964 study by Dr. Hueper in the *Journal of the National Cancer Institute* in which polyurethane foams were implanted in rats. After the foams were implanted either in the animals' neck or abdomen, carcinomas and sarcomas were observed. Degradation of the foams *in vivo* was also observed. SJ Opp. Exh. 60 at 964-986.
- A 1975 study by Dr. John Autian in *Cancer Research* in which 17 chemical varieties of polyurethane were implanted in the abdomens of rats. Autian found that "the data clearly indicate an increased incidence of fibrosarcomas" in rats that received implants. Again, biodegradation of the polyurethanes was observed. *Id.* Exh. 63 at 1063-68.
- A 1976 study by Dr. Autian in *Cancer Research* in which one of the polyurethanes from the 1975 study was implanted in the lungs of rats at varying doses. Autian reported that the frequency of fibrosarcomas increased with increased polyurethane doses and that biodegradation of the polyurethanes had occurred. He concluded that "our data are consistent with a mechanism of biological degradation of the polymer to yield an active carcinogenic compound." *Id.* Exh. 64 at 1069-72.

PUF-coated implants including the Meme implanted in Cagle, degrade after implantation in humans, releasing TDA.

Support

- Lappé Expert Report at 9-10 (citing many of the same studies apparently relied on by Batich).

Studies show that TDA is an animal carcinogen.[12]

Support

- Cancer bioassays (animal studies designed to measure the propensity of an agent to cause cancer in animals) are used by regulatory agencies to estimate the cancer risk to humans. Shanklin Opp. Exh. U at 48-49. In the case of TDA, it appears that cancer bioassays were conducted by feeding TDA to rats or by injecting TDA under a rat's skin. Lappé Report at 7. The bioassays conducted by the National Cancer Institute revealed that TDA produced neoplastic nodules in both male and female rats and mammary carcinomas (breast cancer) in female rats. The bioassays also found TDA to be carcinogenic in female mice. Lappé Report at 7 (citing SJ Opp. Exh. 52 at 841 (NCI Bioassay)).

- Other studies have shown that TDA produces cancer in animals after being painted on the skin, injected under the skin or provided in the animals' diet. Lappé Report at 11-15.

- A Joint Report of the United Nations Environment Programme, the International Labour Organization and the WHO stated that TDA had been found to increase the incidence of mammary tumors in rodents. Lappé Report Exh. P at 119.

TDA is a "probable" human carcinogen.

Support

- Based on the rodent bioassays (*not* the polyurethane implant studies) several groups have concluded that TDA is probably or possibly carcinogenic in humans:

  - The National Toxicology Program ("NTP") has stated that TDA is "reasonably anticipated to be a human carcinogen" and observed that TDA increases the incidence of breast cancer in female rats when administered in the diet. SJ Opp. Exh. 54.

  - In 1986 the EPA found that TDA would likely meet the criteria for classification as a "probable human carcinogen" based on the NTP determination. SJ Opp. Exh. 53.

  - The WHO International Agency for Research on Cancer ("IARC") classified TDA as "possibly carcinogenic to humans" in 1987. SJ Opp., Exh. 74.

- Studies have revised the risk of breast cancer from PUF-coated implants upwards based on biodegradation data.

  - The FDA initially estimated the risk as between 1 and 5 in

[12] A review article proffered by Defendants also states that "[t]here is very little question that TDA . . . [is] carcinogenic in rodents." Lappé MIL Exh. 9 at 235.

1,000,000 (1995). Lappé Expert Report at 15.[13]

- The FDA revised this estimate to 1 in 400,000, which the FDA team concluded presented "an unreasonable risk to health for the patient." (1998). *Id.* at 16-17.

- A study by Sepai *et al.*, which Lappé contends is more accurate, estimated the risk as 1 in 8,431 (1995). *Id.* at 16.

It is "highly likely, beyond a reasonable scientific doubt, that the rapid development of Ms. Cagle's tumor was at a minimum accelerated, and possibly caused, by her exposure to a known animal carcinogen [TDA]." Id. at 20.

Support

- Using data specific to Cagle and concepts derived from *in vitro* PUF biodegradation research,[14] Lappé estimates that 413.6 nanograms of TDA was released from Cagle's implants per day during the first year after implantation. Using that data, the assumed mass of Cagle's breast tissue, and TDA's "potency factor,"[15] Lappé

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[13] This estimate was based on a 1995 study designed by the FDA and Defendant Bristol Myers and conducted by Bristol Myers. Defendants cite this study in their summary judgment motion. *See* SJ Mot. at 4-5 & Exh. 6.

[14] Pages 16 and 17 of Lappe's report, citing the Chu/FDA *in vitro* research, are either incorrect or incomplete, but in any event do not change the basis for or admissibility of Lappe's general causation testimony. Lappe cites a Chu/FDA study as estimating a 1 in 400,000 risk of breast cancer resulting from TDA and claims that Sepai, *et al.* (SJ Opp. Exh. 50) cited this Chu/FDA research in their 1995 publication.

It appears that the scientist's name is Luu, not Chu. Hoan-My Luu and his colleagues at the Center for Devices and Radiological Health for the FDA published a study in 1998 that calculated a 1 in 400,000 risk of breast cancer due to TDA. Moreover, Sepai *et al.* could not have cited this research in their 1995 publication, since it was not published until three years later, in 1998. Luu *et al.* did conduct an earlier study in 1994 that found that PUF implants release TDA *in vitro*. The 1998 study builds upon the 1994 study and calculates the breast cancer risk. Plaintiff provides the Luu/FDA 1994 study as Exhibit 17 to his Opposition to Summary Judgment, but does not provide the Luu/FDA 1998 study, so the Court gave copies of the 1998 study to counsel at the hearing on these motions.

[15] The breast cancer potency factor of TDA was derived in 1989 by Environ Corp. in a study for Defendant Bristol-Myers Squibb Co. SJ Opp. Exh. 36. The (continued...)

concludes that there was a 1 in 3,484 chance that Cagle's breast cancer was due to her implants. *Id.* at 17-19. Since the baseline risk of breast cancer for a person of Cagle's age was apparently 1 in 3,333, Lappé concludes that the additional 1 in 3,484 risk created by Cagle's implants "effectively doubled" Cagle's risk of breast cancer. *Id.* at 29. However, he admits that "by itself, such a numerical exercise does not prove or disprove causation." *Id.* at 19. He later revised that risk assessment, concluding that the risk of developing breast cancer as a result of TDA is approximately 1 in 2 million. Lappe MIL Exh. 1 (Lappe depo.), at 7:9-9:25, 96:22-97:14.[16] The principles Lappe applies from the *in vitro* research can be extrapolated to humans because he cites an *in vivo* study that found an even higher cancer risk than the *in vitro* study upon which he relies. *Id.* at 18 (citing Sepai *et al.*, Exposure to Toluenediamines from polyurethane-covered breast implants, *Toxicology Letters* 77 (1995) 371-378, SJ Opp. Exh. 50).[17]

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[15](...continued)
cancer potency factor "is the incremental risk associated with exposure to one dosage unit of the chemical. It is calculated by applying a low-dose extrapolation model to the available dose-response data, making adjustments if necessary for interspecies extrapolation." *Id.* at 546. The breast cancer potency factor for TDA is 0.21 mg/kg bodyweight/day. *Id.* at 559.

[16] Lappe's risk calculation methodology is similar to that used in the Environ Corp. study (SJ Opp. Exh. 36) and the Luu/FDA 1998 study to estimate an average woman's lifetime risk of developing breast cancer from TDA exposure. His calculation deviates in two respects, however. First, Lappe calculates the risk based on a one-year exposure to the implants rather than a 10-year exposure like the Luu/FDA 1998 study or a lifetime exposure like the Environ Corp. study. Lappe MIL Exh. 1 (Lappe depo.), at 70:5-14. This deviation actually comports more to the actual experience of Toni Cagle and has the effect of reducing the overall risk calculation. *Id.* Second, Lappe employs a tissue-specific risk assessment, using the relative weight of Toni Cagle's breast tissue on the assumption that the breast is a "target tissue" for TDA and that there are enzymes in the breast that activate TDA into its carcinogenic form, as opposed to needing to circulate through the body to be activated by the liver. Lappe Expert Report, at 17. Lappe concedes that this tissue-specific calculation does not follow the routine methodology and is for "illustrative purposes only." Lappe MIL Exh. 1 (Lappe depo.), at 78:14-80:21. Lappe recognizes that if he were to use the established methodology (*i.e.*, no deviation for relative weight of the breasts), the risk of breast cancer from one year of exposure to TDA is 2 in 10 million. *Id.*

[17] Sepai, *et al.* estimated that the risk of developing breast cancer as a result (continued...)

- Lappé cites several factors that would purportedly increase Cagle's risk factor or suggest that his conclusion is sound:
  - Cagle chose some of the biggest implants available, thus, increasing TDA levels.
  - Cancer risks increase relative to the placement of the TDA; here, TDA was administered locally via implantation.
  - Cagle's cancer was extremely aggressive and TDA can accelerate carcinogenesis. In this case Lappé does not provide any support for the proposition that TDA can accelerate tumor growth. Lappé Expert Report at 19-21. Lappe did testify in *Livshits v. Natural Y Surgical Specialties, Inc.*, 1991 U.S. Dist. LEXIS 17245 (S.D.N.Y. 1991), however, that his own work had shown that when animals with preexisting tumors were exposed to TDA, the tumors accelerated and became cancerous. *Id.* at *13-14; SJ Opp. Exh. 61 at 1024-25 (testimony). Lappe testified that there was no human data yet, but hypothesized that the same would be true in humans. *Id.*[18]
  - Pregnancy, coupled with the presence of a carcinogen, increases the risk that the carcinogen will cause mutations leading to cancer.
- Bradford Hill Criteria – a schema used to measure the strength of the association between a causal factor and a given disease. (This is not a test and does not generate new data; essentially, it's just a way of breaking down the causality analysis by asking nine different questions.)

B. Qualifications

Lappé is a toxicologist. Toxicology is "the study of the adverse effects of chemicals on living organisms." *Ref. Manual* at 403 (quoting Casarett and Doull's Toxicology: The Basic Science of Poisons 13 (Klassen ed., 5th ed. 1996)). Toxicologists attempt to determine how a chemical causes disease and at

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[17](...continued)
of TDA is 1,496 in 10 million, or 1 in 6,684 (although Lappe's report at page 16 incorrectly cites Sepai *et al.*'s risk estimate as 1,186 in 10 million, or 1 in 8,431). SJ Opp. Exh. 50 at 708.

[18] The *Livshits* court initially allowed this testimony, but later granted defendant's motion for a new trial because Lappe should only have been permitted to testify to general causation, not specific causation. *Livshits*, at *23.

what doses that chemical produces its effects on humans. *Id.*

Among the cases in which Lappé's testimony was ruled admissible are *Hopkins v. Dow Corning*, 33 F.3d 1116, 1124-25 (9th Cir. 1994), *cert. denied*, 513 U.S. 1082 (1995) and *Livshits*, *supra*. In *Hopkins*, Lappé testified to a "causal connection between Hopkins's implants and [her connective tissue disease]," but it is not entirely clear that he testified to specific causation. 33 F.3d at 1124-25. The issue in that case was whether silicone from the plaintiff's implants had caused her disease. The Ninth Circuit merely noted that "Dr. Lappé is a recognized expert on the immunological effects of silicone in the human body. Specifically, Dr. Lappé testified that his opinion was based on his experience as a toxicologist, his review of medical records and Dow [Corning] studies, and his general scientific knowledge of silicone's ability to cause immune disorders as established by animal studies and biophysical data." *Id.* at 1125. The court did not otherwise comment on Lappe's testimony regarding the precise cause of that plaintiff's illness. Moreover, Defendant distinguishes *Hopkins* on the basis that the alleged agent at issue in that case was silicone. Here, Lappé is testifying as to the alleged carcinogencity of TDA.

In *Livshits*, the plaintiff had received Meme PUF-coated silicone implants. She alleged that the PUF degraded *in vivo* into TDA, which caused her ovarian and uterine cancers and accelerated the development of her breast cancer. 1991 U.S. Dist. LEXIS at *6. On a JNOV motion following a jury verdict for plaintiff, Judge Knapp reviewed Lappé's trial testimony and decided that although Lappé was competent to give testimony about "the possible dangers posed by implantation of the Meme" (general causation), the court had committed plain error in allowing Lappe "to express a diagnostic opinion as to what had caused the acceleration of the cancer in this particular plaintiff's breast" (specific causation). *Id.* at *23. The court noted that Lappé had admitted that he was not licensed to practice medicine and was not qualified to render diagnoses in

humans. Thus, Lappé's general toxicology background did "not qualify him to express an opinion, in terms of medical certainty, as to what was the actual cause of any acceleration of cancer that occurred in this plaintiff's breast." *Id.*

Although Lappé's qualifications are not specific to PUF or TDA carcinogencity, he possesses a strong background in general toxicology. He has a B.A. in Biology. He has a Ph.D in Experimental Pathology, "a cognate field intimately linked to toxicology." Lappé Expert Report at 1. He is a member of the Society of Toxicology. He worked for the FDA reviewing pre-market approval applications submitted by breast implant manufacturers. Given these qualifications – and the absence of evidence that Lappé has any experience making diagnoses in humans – the Court finds, consistent with the *Livshits* court, that Lappé is qualified to render an opinion about general causation, but that he is not qualified to opine on specific causation.

C. Reliability

1. Carcinogenic Properties of PUF vs. TDA

Defendants first contest the reliability of Lappé's testimony by claiming that he has already testified that PUF is non-carcinogenic, that TDA is not a proven carcinogen, and that the cause of cancer is "unknown." Although superficially true, Defendants' argument is disingenuous. Lappé merely testifies that PUF, *before it has broken down to TDA*, is not carcinogenic. Lappé MIL Exh. 1 at 60:8-13 (Lappé Depo.). Additionally, although he stated that "no one can identify the specific cause [of breast cancer in a particular patient, except when BRCA 1 or BRCA 2 genes are present]" *Id.* at 41, generally it cannot be disputed various factors can contribute to and increase one's risk of cancer. (*E.g.*, smoking.) Defendants themselves point out that "[h]ormones play a key role" and that pregnancy and estrogen, too, "play a role in both promoting and initiating breast cancer." Lappé MIL at 6. Lappé does not deny that alternative factors such as pregnancy can contribute to and elevate cancer risks

2. Animal Studies

Defendants also argue that Lappé's reliance on animal studies is methodologically flawed. They argue that (a) the TDA injection and ingestion studies do not prove that TDA causes breast cancer in animals at realistic doses; (b) the polyurethane implant studies (the Hueper and Autian studies) are inconsistent with other studies, have been criticized by other scientists and involved a different polyurethane than the polyurethane used in Cagle's implants and (c) there is no basis to extrapolate from these animal studies to reach any conclusion about whether PUF-coated implants can cause breast cancer in humans.

The first argument can be disposed of quickly. As noted above, several regulatory agencies have determined, based on the bioassays and other studies involving ingestion and inhalation of TDA, that TDA does cause breast cancer in female rats. *See supra* Section III. That those agencies are satisfied that TDA has the same carcinogenic effects in rats that Lappé reports is sufficient for this Court to admit Lappé's testimony in this regard.

The second argument is not a basis to exclude the Hueper and Autian studies. Defendants state that "the scientific community has rejected the notion that Dr. Hueper's studies prove that polyurethane is carcinogenic." Lappé MIL at 11. However, none of the documents Defendants cited supports that proposition. The Clayson and Gibson treatises were not published in time to take Hueper's 1964 findings into account. The Clayson treatise was published in 1962, Lappé MIL Exh. 7 at 76, and the Gibson treatise was published in 1964 but analyzed work Hueper conducted in 1960 only. Lappé MIL at 11 & Exh. 8 at 278-79. It is not clear that the 1994 review article stating that "the only conclusion that can be drawn from the plethora of carcinogenicity studies performed using the rodent model is that this model is clearly not valid for predicting tumorigenesis in

humans," Lappé MIL Exh. 9 at 235, is anything more than a single scientist's opinion. The article was authored by Leonard Pinchuk of the Corvita Corporation, which, as of 1995, had developed a proprietary urethane material to be used in implantable medical devices. *See* "Letter to Shareholders," at http://partisanmgmt.com/corvita/corvita.htm (Letter dated September 15, 1995). There is no indication of whether Pinchuk is affiliated with an academic institution or even whether he has an M.D. or Ph.D. Therefore, the Court cannot conclude that Pinchuk, who apparently founded Corvita (*see* "Dr. Len Pinchuk and Dr. Jeremy Bridge-Cook Elected to Board of Directors at Interface Biologics Inc.," at http://www.g2mpr.com/news/client/Default.asp?articleID=61), is an unbiased investigator qualified to speak or recognized as speaking for the "scientific community." Finally, although Defendants also cite two studies by Brand and Lilla *et al.* in which polyurethane implanted in rats was found not to be associated with cancer, they do not argue that the Hueper and Autian studies are methodologically or otherwise flawed.[19] Indeed, in 1991 Dr. Mishra, Deputy Director of the FDA, stated that the results of the Hueper study "are still valid," and that "our previous conclusions regarding the carcinogenicity of [PUF]-coated breast implants was correct . . . Consequently, [PUF] is not an appropriate material for use in breast implants." SJ Opp. Exh. 12 (Memo to Director of the Office of Device Evaluation) at 366-67. Since there is no reason to believe that the "principles and methodology," *Daubert I*, *supra*, at 595, employed in the Hueper and Autian studies were flawed, contrary studies are not a reason to

[19] Defendants' only argument pertaining to the soundness of the Hueper and Autian studies is that those studies allegedly found solid state tumors only – tumors which do not occur in humans. But the Heuper and Autian studies themselves concluded that the tumors observed were *not* solid state tumors. To the extent that Defendants are arguing that the results of those studies do not support the studies' peer-reviewed conclusion that the tumors observed were not solid state tumors, such a re-analysis is not a basis to exclude the studies.

preclude Lappé from relying on them. *Daubert II*, *supra*, at 1319 n.11 (stating that *Daubert* does not require a majority of the scientific community to agree with the proposed expert's theory or methodology; "methods accepted by a minority . . . may well be sufficient.").

Additionally, that the type of polyurethane used in the Autian study was not precisely the same as the polyurethane in Cagle's implants is not fatal. Autian observed cancer in rats with implanted polyurethane and concluded that "our data are consistent with a mechanism of biological degradation of the polymer to yield an active carcinogenic compound." SJ Opp. Exh. 64 at 1072. Given the additional data indicating that PUF-coated implants degrade in humans to yield TDA – a "probable" carcinogen, as discussed below – Lappé is entitled to rely on the Hueper and Autian studies for the proposition that carcinogenic molecular products released from biodegradation of an implanted polyurethane are capable of causing cancer in animals.

Defendants' final argument, that the animal studies upon which Lappé relies are "not predictive of human cancer," Lappé MIL at 9, is their strongest one, because it raises the difficult issue of whether in this instance it is permissible to rely on the results of animal experiments to demonstrate human causation. The Court concludes below that extrapolation from the animal studies may be permitted on the issue of general causation, but not on the issue specific causation.

In the absence of a solid body of epidemiology, animal studies may contribute to an expert's scientific conclusions as to general causation in humans, *Hopkins*, *supra*, at 1124 (9th Cir. 1994), provided that the expert explains why extrapolation from animals to humans in that instance is proper. *See supra* Section III.B.1. Plaintiff has satisfied that burden regarding the connection between animal studies and general human causation.

Contrary to Defendants' contentions, there is no convincing

epidemiological evidence showing that PUF-coated implants or human exposure to TDA do not cause cancer. As discussed in Section IV.C.1, *supra*, the available human breast implant studies do not shed light on whether PUF-coated implants can cause cancer. Additionally, the occupational studies are far from definitive on the issue of whether TDA released from breast implants can cause cancer. Those studies assess workers in the polyurethane foam manufacturing industry who are known to inhale toluene diisocyanate (TDI), a polyurethane precursor. The studies conclude that exposure to inhaled TDI does not pose a cancer risk. Lappé MIL Exhs. 14-18. Because inhaled TDI may undergo a chemical reaction to produce TDA *in vivo*, Defendants argue, these studies show that polyurethane workers are also exposed to TDA and that therefore TDA also does not pose a cancer risk. The TDI inhalation studies are not definitive, however, because there is evidence that inhaled TDI does not in fact hydrolyze (break down) to TDA. Studies of rats have detected TDA after feeding them TDI, but have not detected TDA after exposure to TDI via inhalation. *Id.* Exh. 13 at 273. And tumors have been observed in rats who ingest TDI but not in rats who inhale the molecule. *Id.* Further studies have shown that when inhaled by rats, TDI becomes bound up with a protein which prevents hydrolysis to TDA. *Id.* Thus, there is a plausible reason having nothing to do with the carcinogenic properties of TDA why exposure to TDI was not found to increase cancer rates in polyurethane workers. *Id.* at 290. Since Cagle was exposed to TDA via implantation of PUF, which *has* been shown to release TDA *in vivo*, the occupational inhalation studies, in which the subjects may not even have been exposed to TDA, are not dispositive on the issue of the carcinogenicity of PUF-coated implants.[20]

[20] Plaintiff and Defendants also cite several studies on hair dye use. *See* Lappé Expert Report at 11; SJ Mot. Exhs 52, 53. The only study actually provided to the Court was the Grodstein *et al.* study of women who used hair dye (continued...)

Therefore, because reliable epidemiological evidence is absent, Lappé's animal testimony would be admissible if Plaintiff demonstrates an analytical basis for extrapolating the TDA results in rodents to humans.

Lappé states that "the applicability and value of some if not all of the animal models of mammary cancer to understanding the dynamics and process of human breast cancer formation is widely recognized and accepted by the scientific community." Lappé Expert Report at 14 (citing R. Calrke [sic], *Animal models of breast cancer: their diversity and role in biomedical research*, 39 Breast Cancer Research and Treatment 1, 1-6 (1996)). Plaintiff also proffers a report of the Office of Science and Technology Policy which stated that studies in rodents "are likely to be relevant to humans" in assessing carcinogenic risks. SJ Opp. Exh. 7 at 278.

By themselves, these general assertions are not sufficient to explain why the particular metabolic, physiologic and other factors that link TDA to cancer in rodents apply to humans. However, that governmental public health organizations in their regulatory decisions have relied on animal studies to conclude that TDA is a "probable" or "possible" carcinogen is sufficient to permit a defensible scientific argument that the mechanisms of cancer induction occurring in the animal studies apply to humans. *See In re Paoli*, *supra*, at 779-81 (district court abused its discretion in excluding animal studies where the EPA had relied on those studies to conclude that PCBs are a "probable" human

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[20](...continued)
between 1976 and 1990. That study found that permanent hair dye is not adversely related to risks of hematopoietic (blood) cancer. SJ Mot. Exhs. 52, 53. Nothing in the study indicates to what extent, if at all, the dyes used by the subjects contained TDA. This is particularly relevant, given that Clairol apparently ceased using TDA in its products in 1971. SJ Opp. Exh. 6. Even if the studied hair dyes contained TDA, the manner of exposure – application to a subject's hair – is so different from the manner of exposure in this case as to make the hair dye studies largely irrelevant to the Court's determinations.

carcinogen, there was reason to think animals react similarly to humans with respect to PCBs, and the epidemiological data was inconclusive and some epidemiological data supported causation).

In 2001, the National Toxicology Program ("NTP"), a program headquartered at the National Institute for Environmental Health Sciences at the National Institutes of Health, *see* http://ntp-server.niehs.nih.gov, and which develops and provides data used to assess human health hazards of environmental exposures, SJ Mot. Exh. 39 at 1 (NTP Report, 57 FR 31721, 1992 WL 164848), classified TDA as "reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals." SJ Opp. Exh. 54 at 848 (Ninth Report). The NTP report also stated that TDA is a degradation product of the PUF used in Meme silicone breast implants and that elevated levels of TDA were detected in the urine and plasma of all patients up to two years after implantation. SJ Opp. Exh. 54 at 850. Based on that information, the NTP concluded that *in vivo* release of TDA from PUF-coated implants "presents an unreasonable health risk to the patients." *Id.* at 850 (citation omitted).[21] Similarly, in 1986 the EPA examined previous work by the NTP and concluded that TDA would likely meet the criteria for classification as a "probable human carcinogen." SJ Opp. Exh. 53 at 843. This is the same classification by the EPA that the *In re Paoli* Court found instructive, stating that "[t]he 'more probable than not' standard employed by the EPA is the same standard that is employed in civil litigation." *In re Paoli*, *supra*, at 780. Finally, the International Agency for Research on Cancer ("IARC") classified TDA as "possibly carcinogenic to

[21] *But see* the NTP's Tenth Report on Carcinogens, published in December 2002 (available at http://ehp.niehs.nih.gov/roc/toc10.html), which includes the same information but omits the sentence stating that PUF-coated implants "present[] unreasonable health risk to the patients."

humans" in 1987. SJ Opp., Exh. 74.[22]

As additional evidence that extrapolation from rodent studies in this case is sufficiently reliable, at least one of the Defendants in this case, Bristol Myers Squibb Co., has represented publicly that animal studies employing PUF implants are relevant to cancer causation in humans. In 1992, Bristol Myers issued a "Fact Sheet" about its own ongoing study of PUF implants in rats in which it stated that "[a] finding of chemically induced tumors distant from the implantation site [in rats] would be relevant to humans." SJ Opp. Exh. 28 at 506.

Finally, although not directly applicable to extrapolation from animals to humans, Lappé not only relies on animal studies showing that injection or feeding TDA to rats causes cancer, he also cites studies that support his theory about the mechanism of release of TDA in the human body. The Hueper study which found occurrences of cancer after implantation of polyurethane foams and the Autian study postulating degradation of polyurethane *in vivo* to yield a carcinogenic molecule are consistent with Lappé's theory that the TDA released from PUF-coated implants can cause cancer.

Defendants cite several cases in which an expert was not permitted to extrapolate the results of animal studies to humans. In *Allen v. Pennsylvania Eng'g Corp.*, 102 F.3d 194 (5th Cir. 1996), the court affirmed the district court's holding excluding causation testimony based on extrapolations from animal studies. Unlike *In re Paoli*, which the *Allen* court distinguished, there was contrary epidemiological evidence, the EPA had not ruled that the substance at issue was a probable carcinogen and the animal studies themselves were unreliable. *Id.* at 197, 197 n.5. In *Hall*, *supra*, where the plaintiff alleged that

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[22] Defendants proffer a 1999 IARC monograph concluding that "[t]here is evidence suggesting lack of carcinogenicity in humans of breast implants made of silicone." This conclusion, based on a lack of convincing evidence that *silicones* biodegrade, does not appear to apply to PUF-coated implants. SJ Mot. Exh. 5 at 309.

silicone from her breast implants had caused her connective tissue disease, the court excluded extrapolations from rodent studies, because the plaintiffs had offered no explanation why the extrapolations were warranted. *Id.* at 1410-11. This case is more like *In re Paoli* than *Allen* and *Hall*, because there is no relevant contrary epidemiological evidence and the EPA and other agencies have extrapolated from the animal studies in their assessments of the risk of TDA to humans.[23]

Therefore, for the reasons discussed above, Dr. Lappé's testimony that animal studies support the proposition that TDA is capable of causing cancer in humans is admissible. The animal studies, however, do not support any conclusion about specific causation. While there may be a scientific basis to

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[23] Defendants also cite *Wade-Greaux v. Whitehall Lab. Inc.*, 874 F. Supp. 1441, 1480 (D.V.I.), *aff'd* 46 F.3d 1120 (3d Cir. 1994) (animal study showing a particular agent to cause birth defects can never be extrapolated to humans absent consistent epidemiological studies); *Lynch v. Merrell-Nat'l Lab.*, 830 F.2d 1190, 1194 (1st Cir. 1987) (same, plus contrary epidemiological evidence available); *In re Agent Orange*, 611 F.Supp. 1223, 1241 (E.D.N.Y. 1985) (animal studies were not reliable because they involved unrealistic high doses in a non-human species and epidemiological evidence available). Those results conflict with *Hopkins,* where the Ninth Circuit found that Dr. Lappé's testimony evidently linking the specific plaintiff's connective tissue disease to silicone from her breast implants, based in part on animal studies, was admissible, because it was "based . . . on the types of scientific data . . . relied upon by medical experts in making determinations regarding toxic causation *where there is no solid body of epidemiological data to review*." 33 F.3d at 1124 (emphasis added). Additionally, *Wade-Greaux* and *Lynch* are distinguishable because Defendants have proffered no evidence that the peculiar difficulties inherent to predicting birth defects via species and dose extrapolation applies to predicting cancer causation.

Finally, Defendants rely on *Lust v. Merrell Dow Pharms., Inc.*, 89 F.3d 594 (9th Cir. 1996), for the proposition that Lappé's animal studies must show a link between PUF-coated implants and the "exact injury alleged by the plaintiff." Lappé MIL at 13. Here, unlike in *Lust*, the NTP *has* acknowledged that TDA rodent bioassays show that TDA can cause the precise injury that Cagle suffered – mammary carcinomas – in female rats.

conclude that PUF-coated implants are generally capable of causing cancer in humans, the animal studies say nothing about the cause of Cagle's cancer. In other words, referring to the testimony described in Section VI.A., Dr. Lappé may testify that:

- Studies have shown that polyurethanes, when implanted in rats, are carcinogenic.
- Studies show that TDA is an animal carcinogen.
- Any TDA released from PUF-coated implants would be a "probable" human carcinogen.[24]

Lappe may not testify, however, that it is "highly likely, beyond a reasonable scientific doubt, that the rapid development of Ms. Cagle's tumor was at a minimum accelerated, and possibly caused, by her exposure to a known animal carcinogen [TDA]." Lappe Expert Report, at 20. First, he is not qualified to opine on specific causation. *See*, *e.g.*, *Livshits*, *supra*. Second, to the extent his revised calculation that the risk of developing breast cancer as a result of TDA is 2 in 10 million is probative, it may be used only to show general causation.[25] Third, Lappe may not testify that his own research shows that TDA can accelerate a preexisting tumor because there is no evidence that he has published that research or subjected it to peer review. Nor has his acceleration theory gained "general acceptance" in the scientific community. Thus, Plaintiff has not met his burden of establishing that Lappe's acceleration testimony meets *Daubert*'s

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[24] Lappé may rely on Dr. Batich's testimony that the PUF-coated breast implants hydrolyze after implantation and release TDA.

[25] It is questionable whether this extremely slight risk assessment actually supports Plaintiff's position. In any event, Lappe's breast tissue-specific calculation that the risk of developing breast cancer as a result of TDA is 1 in 2 million is unreliable because it is not based on an accepted methodology. The accepted risk assessment methodology uses the entire weight of the body in the calculation, not the relative weight of certain target tissues. Thus, Lappe's calculation of 2 in 10 million is probative, while his calculation of 1 in 2 million is not. *See* footnote 16, *supra.*

requirements for reliability and admissibility. *Daubert I, supra,* at 593-94; Fed. R. Evid. 702.

D. Usefulness

This requirement is satisfied–barely–but only to the extent that Lappé's general causation testimony is a necessary component of Plaintiff's case.

E. Conclusion

Lappé, a toxicologist with no expertise in making individualized diagnoses, is qualified to testify about whether breast implants are capable of causing breast cancer in humans and in doing so he may extrapolate from animal studies. But he is not qualified to render opinions about what caused Toni Cagle's breast cancer or whether her PUF implants could have accelerated any preexisting cancer she may have had.

VII. Dr. Douglas Shanklin (pathologist)

Dr. Shanklin proposes to testify about both general and specific causation. His testimony is based on his analyses of tissue slides obtained from Cagle's tumor, calculations about when Cagle's cancer was initiated and testimony about certain factors specific to Cagle that increased her likelihood of contracting breast cancer.

A. Proposed Testimony[26]

Basically, Shanklin will testify that "it is my opinion that the TDA contributed to [Cagle's] breast cancer by promoted [sic] or accelerating the underlying DCIS [ductal carcinoma *in situ*] and causing it to become more rapidly invasive and aggressive . . .." Shanklin Opp. Exh. R (second Shanklin Decl.) ¶

[26] Shanklin's report contains information that is not relevant to this case. For example, he states that he intends to testify about various properties and effects of silicone. Opp. Exh. D ("Shanklin Report") at 48. Plaintiff asserts that Shanklin will not be offering any opinion linking silicone to breast cancer in this case. Shanklin Opp. at 7 n.2.

15.

General Causation

TDA is a "potent animal carcinogen" that is "reasonably anticipated to cause cancer in humans." Id. ¶ 14.

Support

- Shanklin relies on the same studies, data and evaluations by risk assessment agencies as Lappé.

"The carcinogenic potential of polyurethane breakdown products was sufficiently known" prior to May 1989 when Cagle received her implants as to make the cessation of clinical use of such products "the only prudent course of action." Shanklin Opp. Exh. D ("Shanklin Report") at 49.

Support

- Shanklin relies on the same studies, data and evaluations by risk assessment agencies as Lappé.

When PUF foam is implanted into the human body, the body's immune system reacts to the foreign matter by creating a fibrous scar around the implants, which becomes "the active zone of . . . irritation and stimulation" of the immune system. This leaves both the site of the implants and the body as a whole susceptible to disease. Id. at 48.

Support

- Shanklin has published several articles about immune responses to silicone implants in humans. *See, e.g.*, *T cell-mediated response to silica in silicone breast implant patients*, 210 Current Topics in Microbiology and Immunology 227-36 (1995) (Shanklin Opp. Exh. A, Publication No. 241); *Immunologic stimulation of lymphocytes in silicone gel breast implant patients*, Assoc. of Medical Laboratory Immunologists, 7th Annual Meeting (1994) (*Id.*, Publication No. 226).

- He has not published anything about the immune effects of PUF-coated implants, but intends to write an article about the body's reaction to PUF implants based on his own research. Shanklin MIL Exh. 1 (Shanklin Depo.) at 34:13-36:11. *See infra* Section VII.B.

Factors Rendering it More Likely Than Not that Cagle's Cancer was Caused By Her Implants

Cagle's tumor was a squamous cell carcinoma that is "one of the most rare and . . . most aggressive" breast cancers. Shanklin Opp. Exh. B ¶ 6 (third Shanklin Decl.)

Support

- He examined tissue slides from Cagle's tumor. *Id.*

Cagle's family cancer history does not indicate that her cancer was

hereditary. Shanklin Report at 50-51.

Support

- Shanklin examined Cagle's reported family history and states that kidney cancer, from which her mother suffered, SJ Opp. Exh. 3 at 8:17-19 (Cagle Depo.), is not related to breast cancer. He also notes that Cagle was survived by two sisters who have not contracted breast cancer. Shanklin does not explain why the breast cancer of Cagle's maternal half-aunt, *id.* at 9:13-16, and the stomach cancer of Cagle's paternal aunt, *id.* at 11:6-17, are not relevant to this analysis. He does explain that breast cancer can be linked to a family history of breast cancer or female reproductive cancers. In a later declaration, Shanklin also states that Cagle's maternal half-aunt's breast cancer "put her at a slightly higher risk of developing cancer." Shanklin Opp. Exh. R **(**second Shanklin Decl.**)** ¶ 17.

A pregnancy suppresses a woman's immune system temporarily. This change can make a woman more susceptible to cancer. Shanklin Opp. Exh. B **(**third Shanklin Decl.**)** ¶ 8. *Additionally, estrogen and progesterone, which regulate breast growth and cell division, are produced in increased quantities during pregnancy. A mammary tumor cell with receptors for those hormones would be expected to grow in response. Id.*

Support

- Shanklin represents that there is a "fairly extensive" body of literature on the relationship between pregnancy and cancer. He admits, however, that he is not aware of any publication that addresses the effect of an implant during pregnancy on cancer risk. Shanklin MIL Exh. 1 (Shanklin Depo.) at 80:11-81:17.

In any event, however, Dr. Shanklin found that Toni Cagle's tumor had negative estrogen and progesterone receptors. Id. at 79:24-80:10 and 103:22-104:7.[27]

A chemical carcinogen located in a pregnancy-associated high cell growth milieu "would be expected to have a tumor promoting effect." Shanklin Opp. Exh. R **(**second Shanklin Decl.**)** ¶ 13.

Support

- Plaintiff has proffered abstracts from several published *in vitro* studies showing an association between cell proliferation and chemical-induced mutations. Two of those studies were experiments involving TDA. Shanklin Opp. Exh. Q at 155-60.

[27] Although Toni Cagle's tumor was receptor-negative, Shanklin states that the estrogen and progesterone receptors may have been reported as negative because "undifferentiated tumors [like Cagle's] tend to lose their receptor specificity." Shanklin MIL Exh. 1 (Shanklin Depo.) at 80:6-10.

It is probable that Cagle's tumor was induced through an "instantaneous hit" after implantation. Shanklin MIL Exh. 1 (Shanklin Depo.) at 86:14-17; *see also* Shanklin Report at 49.

Support

- Shanklin calculates the amount of time that would have elapsed from induction of Cagle's cancer to removal of her tumor based on the type of cancer and the size of her tumor. He concludes that Cagle's cancer was induced almost immediately after implantation.

Alternatively, TDA from the implants accelerated a preexisting tumor and caused it to become more rapidly invasive and aggressive. Shanklin Opp. Exh. R (Shanklin Decl.) ¶ 15.

Support

- Shanklin provides absolutely no support for the proposition that TDA can accelerate a preexisting cancer. He cites no *in vitro* or animal studies showing that TDA has such cancer-promoting properties, nor does he explain why he can infer such properties from the other TDA data. In addition, Shanklin cannot rely on Dr. Lappe's testimony about his unpublished tumor acceleration research in *Livshits*, *supra*, because it is unreliable and inadmissible under *Daubert*. *See* Section VI.C, *supra*.

B. Qualifications

Shanklin is a physician and pathologist. According to Shanklin, pathology is the study of disease. It is "a science of recognition and classification out of which prognosis and treatment principles are developed and derived." Shanklin Opp. Exh. B ¶ 7 (third Shanklin Decl.). It appears from his somewhat conclusory declaration that a pathologist can reach a determination about disease in a particular patient by examining evidence derived from that patient (e.g. medical history, biopsy slides, physical examination) and comparing that information with previous personal experience, journal articles and textbooks. *Id.* ¶ 7. He also states that "[p]athologists are generally aware of the role of animal experimentation in the study of disease." *Id.* ¶ 8.

Shanklin has published hundreds of articles in scientific journals, some of which pertain to immunologic effects of silicone-containing devices. Shanklin admits that he has written only one article touching on the immunological effects

of PUF-coated devices. Shanklin MIL Exh. 1 (Shanklin Depo.) at 31:24-32:19. That article is *Dynamics of Wound Healing after Silicone Device Implantation*, 66 Experimental Molecular Pathology 26-39 (1999). Shanklin Opp. Exh. A at 25, Publication No. 275. Shanklin does not appear to have written any article about a link between PUF-coated implants and cancer or about the carcinogenicity of TDA. Shanklin testified in August 2002, however, that his research group is working on "a definitive article on the body's reaction to [PUF]-coated implants." Shanklin MIL Exh. 1 (Shanklin Depo.) at 35:20-36:11. That article will not be specifically about the relationship between polyurethane and cancer. *Id.* at 35:20-23.[28]

Defendants argue that Shanklin is not qualified to render his proposed opinions. They point out that while Shanklin is a board-certified pathologist, he has not taken special boards in the forensic, clinical or immunologic pathology subspecialties. Shanklin MIL Exh. 19 at 83:1-84:3 (Shanklin testimony in *Toole*). However, the lack of sub-specialization does not render Shanklin's testimony inadmissible. Shanklin's general pathology experience qualifies him to testify about the nature and causes of Cagle's disease. That Shanklin does not have certain sub-specialty credentials affects the weight of his testimony and not its admissibility. *Holbrook*, *supra*, at 782.

Defendants also argue that Shanklin is not qualified to opine that TDA is carcinogenic in animals and potentially carcinogenic in humans. However, given that pathologists "are generally aware of the role of animal experimentation in the study of disease," Shanklin Opp. Exh. B **(**third Shanklin Decl.**)** ¶ 8, Shanklin is qualified to testify about the same animal studies relied on by Lappé and to conclude that TDA is capable of causing breast cancer in humans. *See supra* Section VI.C.

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[28] At the hearing on these motions the parties advised the Court that they do not believe that Dr. Shanklin has written or published such an article.

The real issue with Shanklin is not his qualifications, but whether his testimony is sufficiently reliable.

C. Reliability

1. General Causation

Shanklin's proposed general causation testimony relies on the same foundation and studies as Dr. Lappé in concluding that TDA is a known animal carcinogen. Plaintiff proffers the same regulatory assessments as Lappé relied on to support Shanklin's testimony that TDA is capable of causing breast cancer in humans. Therefore, Shanklin's general causation testimony is reliable for the reasons discussed in Section VI.C.2.

Shanklin's testimony about the immunological effects of PUF-coated implants – that a scar is created leaving the implant site susceptible to disease – is sufficiently reliable to be admitted. Shanklin has published several articles about immune responses to silicone implants in humans, but he has not published anything about the effects of PUF-coated implants. However, as noted above, he intends to write "a definitive article on the body's reaction to [PUF]-coated implants" based on over fifty cases he has studied, though he still had not written any such article as of April 9, 2004, the date of the hearing on these motions. Given Shanklin's representation that he studies tissue diseases that arise when foreign materials are implanted in the human body, and that his field of pathology is routinely based on observations of patients and their symptoms, Shanklin is entitled to describe for the jury what he has observed in his fifty-patient sample.

2. Specific Causation

Although he does not say so, Shanklin's specific causation conclusion – that TDA from Cagle's implants either caused or accelerated her breast cancer – is essentially based on the technique of differential diagnosis. As explained in Section III.B.2, *supra*, differential diagnosis is the process of elimination that doctors routinely use to identify the most likely cause of a particular individual's

illness. Shanklin reached his conclusion about the cause of Cagle's breast cancer based on his examination of tissue slides showing that the tumor was squamous cell carcinoma, her medical history and her family history of cancer, the size of her tumor and the fact that she became pregnant shortly after receiving her implants.

Shanklin's differential diagnosis is based on three premises. First, he notes that Cagle's pregnancy and the fact that she had not been pregnant before implantation caused her to be more susceptible to the harmful effects of a mutagen such as TDA. Shanklin Opp. Exh. R **(**second Shanklin Decl.**)** ¶ 13. Second, he concludes that the size of the tumor removed from Cagle's breast is consistent with a cancer induced after Cagle received her implants. Shanklin MIL Exh. 1 **(**Shanklin Depo.**)** at 82:11-86:2. Third, he observes that Cagle was afflicted with one of the most rare and most aggressive breast cancers**,** squamous cell carcinoma. Shanklin Opp. Exh. B **(**third Shanklin Decl.**)** ¶ 6.

"[A]n expert must rule out other potential sources of the patient's condition in order for differential diagnosis testimony to be admissible." *Hall*, *supra*, at 1414 (citing *Conde v. Velsicol Chem. Corp.*, 24 F.3d 809, 814 (6th Cir. 1994); *In re Paoli*, *supra*, at 759). There are many factors that are believed to potentially cause breast cancer, including age of first menarche, genetics, geographic location or exposure to radiation, *see* Shanklin Opp. Exh. U at 45-46. Shanklin's conclusions do not explicitly rule out other potential causes of Cagle's cancer, but they do nevertheless allow him to opine that it was more probable than not that it was Cagle's exposure to TDA – and not her exposure to other genetic or environmental cancer-causing factors – that caused her breast cancer**.**[29]

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[29] Shanklin's second declaration, Shanklin Opp. Exh. R at ¶¶ 9-12, sets forth the breast cancer causes (BRCA 1, BRCA 2, and P-35 genes) and risk factors (ionizing radiation, exogenous hormones, environmental factors like exposure to

(continued...)

The basis for Shanklin's first premise – that Cagle was more susceptible to the effects of TDA because she was pregnant – is as follows. Shanklin represents that it is well-known that hormones released during pregnancy stimulate mammary cell growth and that there is a "fairly extensive" body of scientific literature about the relationship between those proliferating cells and cancer. Shanklin MIL Exh. 1 (Shanklin Depo.) at 80:11-81:17. Plaintiff also provides abstracts from several published *in vitro* studies that show an association between cell proliferation and mutations caused by chemicals such as TDA. *See* Shanklin Opp. Exh. Q at 115-60. Shanklin also states that the immune system is temporarily suppressed during pregnancy so that the woman's body will not reject the fetus. Shanklin Opp. Exh. B (third Shanklin Decl.) ¶ 8. Plaintiff also provides an article explaining that a woman's first birth has a protective effect against breast cancer. The earlier a woman has her first birth, the lower her lifetime risk of breast cancer. *Id.* Exh. N. Cagle had not been pregnant before receiving her implants. From these premises, Shanklin concludes that the TDA in Cagle's implants "would be expected to have a tumor promoting effect." *Id.* Exh. R (second Shanklin Decl.) ¶ 13.

Although Shanklin states that there is "a fairly extensive body of literature" supporting a link between hormonal changes during pregnancy and cancer, he

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[29](...continued)
organochlorine pesticides). The only risk factors Defendants raise are Toni Cagle's underlying DCIS and family history of cancer. *See* Defendants' Statement of Uncontroverted Facts and Conclusions of Law, ¶¶ 2, 5. Dr. Shanklin explains that DCIS only increases a woman's risk of cancer by 30-50% 10 to 18 years later and that even then, the survival rate is almost 100%. SJ Opp. Exh. 14 (first Shanklin Decl.) ¶ 3. He also addresses family history and rules it out as the cause of Toni Cagle's cancer. Shanklin Report at 50-51; Shanklin Opp. Exh. R (second Shanklin Decl.) ¶ 17. Shanklin also rules out pregnancy hormones since the tumor was estrogen and progesterone receptor negative. Shanklin MIL Exh. 1 (Shanklin Depo.) at 79:24-80:10 and 103:22-104:7. There is no evidence in the record that Cagle was exposed to ionizing radiation or organochlorine pesticides.

admits that he is not aware of any publication that addresses the effect on cancer risk of implants during pregnancy. Shanklin MIL Exh. 1 (Shanklin Depo.) at 80:11-81:17. He cites no authority for the proposition that a pregnancy or a late first birth increases the likelihood of breast cancer *caused by TDA*. The articles Plaintiff cites show increases in breast cancer during and for the first few years after a pregnancy generally, not only during pregnancies of women known to be exposed to TDA. Nonetheless, Shanklin would be entitled to testify that there is evidence that pregnancy can lead to a suppression or reduction in the immune system.

Shanklin's second conclusion – that the size of Cagle's tumor is consistent with a cancer induced after she received her implants – is based on a calculation supposedly showing that the initiation date of Cagle's cancer was immediately after she received her implants. He testified that in his opinion "there were no cancer cells in Miss Cagle's breast" on the day before the implantation, Shanklin MIL Exh. 1 (Shanklin Depo.), at 82:11-24. Because there exists a latent period between exposure to a potential carcinogen and detectable cancer symptoms (*e.g.*, discovery of a lump), scientists count backwards from the date of cancer detection to determine the hypothetical date that the cancer was induced. To this end, scientists employ "doubling time" calculations. The doubling time of a tumor is the amount of time it takes for its component cells to double in number. When enough doubling cycles have occurred, the tumor is large enough to be detectable as a "lump" in a woman's breast.

Using a doubling time of 23 days – the "most aggressive" (*i.e.*, short) doubling time, associated with extremely aggressive cancers – Shanklin calculated that Cagle's tumor underwent about 19 doubling cycles during the 451 day period between Cagle's receipt of implants and the removal of her two-centimeter tumor. Shanklin MIL Exh. 1 (Shanklin Depo.) at 82:11-86:2. Shanklin appears to conclude that this was a sufficient number of doubling cycles

for a tumor induced immediately after implantation to reach the size of the tumor found in Cagle's breast. (As he put it, "We're talking about an instantaneous hit . . ." *Id.* at 86:16.)[30]

The parties dispute vigorously whether Shanklin's methods of calculating doubling times are sound. Defendants argue that a 451 day latency period is unrealistically short. They evidently believe that the latency period is the time between exposure to a carcinogen and the onset of tumor growth. *See* Shanklin MIL Exh. 1 (Shanklin Depo.) at 86:3-17(Q: Now, that calculation assumes that the very first cancer cell would have been . . . created in [Cagle's body] on May 2, 1989 [the day Cagle received her implants], right? A: Okay. . . . Q: So essentially no latency whatsoever."). The latency period also has been described as the time between exposure to a carcinogen and "symptomatic manifestation of the resulting cancer." *Id.* Exh. 16 at 346. Defendants have proffered an article explaining that the latency period between initial exposure to low levels of carcinogens in the environment and symptoms of cancer can span many years. *Id.* at 346-47.[31] Plaintiff points to a high dose animal study in which a latent period

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[30] There is support for the proposition that TDA could have been released from Cagle's implants shortly after implantation. In one study, researchers found TDA levels ranging from 0.25 to 4.1 ng/ml in patients' urine post-implantation. The researchers also found elevated TDA levels (about 38 ng/ml) in patients' redon drainage samples during the days immediately following implantation. Sepai, *et al.*, *Exposure to toluenediamines from polyurethane-covered breast implants*, 77 Toxicology Letters 373-75 (1995) (Batich Opp. Exh. T).

[31] Although exposure to low levels of chemicals in one's environment is different from implantation of a device secreting that chemical, Defendants' article does show that Cagle's cancer may not have been caused by her implants, but rather by exposure to some chemical in her environment several years before. Indeed, based on the levels of TDA the Sepai authors found in patients' urine post-implantation, they concluded that "the possible added risk [of TDA] is much lower than the risk of breast cancer in the general population." Batich Opp. Exh. T, at

(continued...)

in mice of forty to fifty weeks was observed, Shanklin MIL Exh. 12 at 322.

The real problem with Shanklin's conclusion is that by his own admission, a tumor generally must undergo 30 doubling cycles even to reach a palpable size of only one centimeter. Shanklin MIL Exh. 1 (Shanklin Depo.) at 41:14-42:4, 44:7-45:6. According to Dr. Shanklin's calculations regarding Cagle's tumor (using a 23 day doubling time), it went through only about 19 doubling cycles–increasing from one cancer cell immediately after implantation to a more than two-centimeter tumor in just 451 days.[32] *Id.* at 84:17-85:18. Assuming a doubling time of 23 days multiplied by 30 doubling cycles, the tumor would not have grown to be even one centimeter until 690 days after she received her implants.[33] Using Shanklin's own underlying assumptions, in short, 19 doubling cycles just would not be sufficient to create a palpable one-centimeter tumor, let alone the two-centimeter tumor Toni Cagle's doctors discovered. Thus, the methodology Shanklin employs to conclude that Toni Cagle's breast cancer was induced after implantation is unreliable and inadmissible under *Daubert* and Fed.

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[31](...continued)
377. Therefore, while Shanklin's calculation may demonstrate an *association* between Cagle's implants and her cancer, it does not explicitly eliminate or reduce the possibility that something else caused Cagle's cancer.

[32] The pathology report actually revealed two masses, one measuring 2.5 x 1.5 x 1.3 centimeters and the other measuring 3.5 x 2.3 x 1.3 centimeters. Shanklin Opp. Exh. J.

[33] This argument appears at page 17 of Defendants' MIL and Plaintiff does not address it in his Opposition to the MIL. He does argue that in *Livshits, supra*, Dr. Shanklin used the same technique to conclude that a two centimeter tumor the plaintiff discovered 15 months (about 450 days) after receiving her implants was either caused or promoted by her implants since the tumor was not palpable at the time of implantation. Shanklin Opp. at 23 (citing *Livshits* at *21). That testimony is easily distinguishable. Apart from the fact that the trial court in *Livshits* granted a new trial, here Shanklin has not merely opined that Toni Cagle's tumor was not "palpable" on the day of her implantation surgery, but has instead declared that there was not even one cancer cell in her breasts before such surgery.

R. Evid. 702.

Shanklin's third conclusion is that Cagle contracted squamous cell carcinoma, an extremely rare and aggressive type of breast cancer. Cagle's original diagnosis was poorly differentiated, infiltrating ductal carcinoma ("IDC") with ulceration and necrosis. Shanklin Opp. Exh. J at 83. IDC accounts for up to eighty percent of all breast cancers. Shanklin MIL Exh. 3 at 163:3-164:7 (*Brusca Daubert* hearing). Although Plaintiff admitted in his response to Defendants' Statement of Uncontroverted Facts and Conclusions of Law ("SUF") that "Mrs. Cagle had infiltrating ductal carcinoma of the right breast," he added that while IDC is common, "it is not common for the cancer to be non-differentiated, ulceration and necrosis [sic]." SUF ¶¶ 3-4. Dr. Shanklin always maintained that even if Cagle's tumor was IDC, it was poorly differentiated and much more aggressive than most IDC. Shanklin MIL Exh. 1 (Shanklin Depo.) at 67:1-68:18; SJ Opp. Exh. 14 (first Shanklin Decl.) ¶ 1; Shanklin Opp. Exh. R (second Shanklin Decl.) ¶ 3. The unusual characteristics of the tumor (poor differentiation with ulceration and necrosis) led Dr. Shanklin to testify in his first declaration that it had "features of a rare form of cancer: squamous cell carcinoma," SJ Opp. Exh. 14 at ¶ 1, a view that he later confirmed and "extended" when he saw tissue slides of the lymph node metastases for the first time. Shanklin Opp. Exh. B (third Shanklin Decl.) ¶ 6. Shanklin's pathology background certainly qualifies him to make individualized disease diagnoses on the basis of tissue slides, and contested facts must be construed in favor of the Plaintiff, so the Court accepts Shanklin's determination that Cagle suffered from a squamous cell carcinoma, at least for purposes of these motions.[34]

[34] Defendants argued at the hearing on these motions that it would be unfair not to hold Plaintiff to his statements in the SUF. The Court disagrees, especially as Dr. Shanklin's final diagnosis of squamous cell carcinoma was at least hinted at (continued...)

However, that Cagle's cancer was rare and aggressive also does not prove anything about whether it was caused by her implants. Plaintiff proffers no data tending to suggest that a squamous cell carcinoma is more likely to have been caused by TDA than by other potential cancer-causing factors. Indeed, the animal studies Plaintiff relies on do not appear to have discovered squamous cell carcinomas in rats and mice exposed to TDA.

Shanklin also proposes to testify that if TDA did not cause Cagle's cancer, it accelerated the growth of a preexisting tumor and caused it to become more rapidly invasive and aggressive. Shanklin Opp. Exh. R **(**second Shanklin Decl.**)** ¶ 15. However, he has provided no support for the proposition that TDA can "accelerate" a preexisting cancer. He cites no *in vitro* or animal studies showing that TDA has been shown to cause a pre-existing tumor to become more invasive or aggressive. The studies upon which Plaintiff's experts rely show an increase in the incidence of cancer in TDA-exposed animals, but not possible effects of TDA on rates of cancer growth in animals with preexisting cancers. In addition, Shanklin cannot rely on Dr. Lappe's testimony about his tumor acceleration research in *Livshits*, *supra*, because it is unreliable and inadmissible under *Daubert*. *See* Section VI.C, *supra*.[35]

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[34](...continued)
in his first declaration, which stated that the tumor had features of squamous cell carcinoma. In addition, Plaintiff relies heavily on the "rare and aggressive" characteristics of the tumor, qualities Dr. Shanklin contends were present even before he saw all of the tissue slides.

[35] Although Lappé is not qualified to opine on specific causation, *see* Section VI.B *supra*, he testified that although it is possible that the presence of TDA caused Cagle's tumor, it is more likely that the TDA accelerated the growth of a pre-existing tumor. SJ Mot. Exh. 12 (Lappé Depo.) at 31:17-32:18. Shanklin, on the other hand, believes that TDA probably initiated Cagle's tumor, rather than promoting the growth of a pre-existing one. *Id.* Exh. 1 (Shanklin Depo.) at 108:3-13.

Moreover, Plaintiff provides no specific data about possible carcinogenic effects of the amount of TDA to which Cagle was theoretically exposed. The animal studies upon which Shanklin and Lappé rely employed significantly higher doses of TDA. While those studies were sufficient for regulatory agencies to conclude that TDA is capable of causing cancer in humans, the evidence for the proposition that the dose of TDA Cagle received created so high a cancer risk that it is more probable than not that it was TDA – and not other breast cancer risk factors – that caused Cagle's cancer is thin.[36]

To summarize, Shanklin may testify that Cagle's pregnancy may have caused her to be more susceptible to carcinogens and that her tumor was a squamous cell carcinoma. He may not testify, however, that his calculations show that the tumor was induced immediately after she received the implants because that testimony is unreliable. Even when using the shortest doubling time, the tumor could not have gone through enough doubling cycles to reach its ultimate size of more than two centimeters. Shanklin also may not testify in the alternative, that TDA from Toni Cagle's implants accelerated her breast cancer because he does not cite any support for that proposition and may not rely on Dr. Lappe's research.

D. Usefulness

Shanklin has adequately supported his proposed testimony that pregnancy increases a woman's susceptibility to cancer and that proliferating cells – such as

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[36] However, the testimony and evidence provided by Lappe about the amount of TDA to which Cagle may have been exposed does exceed (by more than two times) the maximum allowable exposure of 0.2 micrograms per day under the California Safe Drinking Water and Toxic Enforcement Act of 1986, and a low dose of a carcinogen can produce cancer, especially if the person has any sort of predisposition. Lappe Expert Report at 18, 25.

breast cells during a pregnancy – are more susceptible to the mutagenic effects of chemical carcinogens. Similarly, Shanklin's revised diagnosis of what kind of cancer Cagle had satisfies the reliability threshold.

E. Conclusion

Dr. Shanklin's testimony about general causation would be admissible, although it overlaps with Dr. Lappe's testimony. However, since neither Shanklin nor any of Plaintiff's other witnesses can reliably testify that it is more likely than not that Cagle's cancer was caused or accelerated by TDA released from her implants, the admissible portion of his proffered testimony will not be useful for the jury in assessing specific causation in this case. Accordingly, the testimony must be excluded.

VIII. Defendants are Entitled to Summary Adjudication on Bradley Cagle's Claims

A. Summary Judgment Standard

Federal Rule of Civil Procedure 56(c) provides for summary judgment when "the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law." The moving party bears the initial burden of demonstrating the absence of a "genuine issue of material fact for trial." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 256 (1986). A fact is material if it could affect the outcome of the suit under the governing substantive law. *Id.* at 248. The burden then shifts to the nonmoving party to establish, beyond the pleadings, that there is a genuine issue for trial. *Celotex Corp. v. Catrett*, 477 U.S. 317, 324 (1986).

When the non-moving party bears the burden of proving the claim or defense at trial, the moving party can meet its burden by pointing out the absence of evidence from the non-moving party. The moving party need not disprove the

other party's case. *See Celotex*, 477 U.S. at 325. Thus, "[s]ummary judgment for a defendant is appropriate when the plaintiff 'fails to make a showing sufficient to establish the existence of an element essential to [his] case, and on which [he] will bear the burden of proof at trial.'" *Cleveland v. Policy Mgmt. Sys. Corp.*, 526 U.S. 795, 805-06 (1999) (*citing Celotex*, 477 U.S. at 322).

When the moving party meets its burden, the "adverse party may not rest upon the mere allegations or denials of the adverse party's pleadings, but the adverse party's response, by affidavits or as otherwise provided in this rule, must set forth specific facts showing that there is a genuine issue for trial." Fed. R. Civ. P. 56(e). Summary judgment will be entered against the non-moving party if that party does not present such specific facts. *Id*. Only admissible evidence may be considered in deciding a motion for summary judgment. *Id*.; *Beyene v. Coleman Sec. Serv., Inc.*, 854 F.2d 1179, 1181 (9th Cir.1988).

"[I]n ruling on a motion for summary judgment, the nonmoving party's evidence 'is to be believed, and all justifiable inferences are to be drawn in [that party's] favor.'" *Hunt v. Cromartie*, 526 U.S. 541, 552 (1999) (quoting *Anderson*, 477 U.S. at 255). But the non-moving party must come forward with more than "the mere existence of a scintilla of evidence." *Anderson*, 477 U.S. at 252. Thus, "[w]here the record taken as a whole could not lead a rational trier of fact to find for the nonmoving party, there is no genuine issue for trial." *Matsushita Elec. Indus. Co., Ltd. v. Zenith Radio Corp.*, 475 U.S. 574, 587 (1986) (citation omitted).

B. Analysis

Plaintiff would have the burden at trial of proving both general causation (*i.e.*, that PUF implants have the capacity to cause breast cancer in humans) and specific causation (*i.e.*, that Toni Cagle's breast cancer was caused by her PUF implants). *In re Hanford Nuclear Reservation Litig.*, *supra*, at 1133-34. Plaintiff has met his burden of creating a genuine dispute of material fact regarding

general causation. If the following facts were found, believed, and construed favorably to Plaintiff, they would permit a reasonable jury to find that PUF implants have the capacity to cause breast cancer in humans:

(a) One epidemiological study provides "suggestive evidence" of a causal link between PUF-coated implants and cancer, and the studies involving silicone implants are not instructive (Neugebauer).

(b) The polyurethane coating of PUF-coated implants biodegrade after implantation in humans (Batich).

(c) The degradation products of the PUF-coating include TDA (Batich).

(d) TDA is known to be carcinogenic in animals and is a "probable" human carcinogen (Lappé and Shanklin).

Plaintiff has failed to meet his burden, however, of showing that there is a genuine issue for trial regarding specific causation. He has proffered the expert testimony of Lappe and Shanklin for the proposition that the amount of TDA likely released from Cagle's implants, coupled with her pregnancy and the rare type of breast cancer she suffered, make it more likely than not that her tumor was caused or accelerated by TDA released from her implants. But that testimony fails to meet the standards for admissibility. *See Daubert*, *supra*; Fed. R. Evid. 702. Dr. Lappé is not qualified to render a particularized diagnosis of the cause of Cagle's illness and his calculations and assumptions in that regard are unsupported. Although in principle Dr. Shanklin *is* qualified to render an opinion about what caused Cagle's breast cancer, his methodology for concluding that the tumor was induced immediately after implantation is unreliable and he cites no support for his alternative proposition that TDA accelerated Cagle's cancer. Plaintiff has failed to come up with evidence creating a genuine issue regarding specific causation. Fed. R. Civ. P. 56(e).

IX. Conclusion

For the foregoing reasons, the Court GRANTS IN PART and DENIES IN PART Defendants' motions *in limine* to exclude the testimony of Dr. Richard

Neugebauer,[37] Dr. Christopher Batich,[38] Dr. Marc Lappe,[39] and Dr. Douglas Shanklin.[40]

Defendants are entitled to summary adjudication on claims one through seven, nine and ten of the Amended Complaint.[41] As noted in footnote 1, *supra*, this order does not address claim eight, which was brought by Bradley Jr. By not later than May 10, 2004 the parties are to file a single, jointly-prepared Status Report as to their positions and intentions concerning whether that claim is at least theoretically viable in light of this ruling and–even if Plaintiff thinks it is viable–whether they can agree that, pending a ruling from the Ninth Circuit, Plaintiff will dismiss Bradley, Jr.'s claims without prejudice, provided that Defendants enter into an appropriate tolling agreement. After receiving that Status Report, the Court expects to order Defendants' counsel to lodge a proposed judgment.

IT IS SO ORDERED.

DATE:

A. Howard Matz
United States District Judge

[37] Docket No. 117.

[38] Docket No. 120.

[39] Docket No. 114.

[40] Docket No. 118.

[41] Docket No. 95.