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UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF MASSACHUSETTS

Brian K. Milward and Linda J. Milward	*	
v.	*	Civil Action
Acuity Specialty Products Group, Inc., et al.	*	No. 1:07-cv-11944-GAO

Deposition of David W. Pyatt, Ph.D.

Thursday, February 19, 2009

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MORNING SESSION
9:03 a.m.

DAVID W. PYATT, Ph.D.,
having been first duly sworn on oath,
was examined and testified as follows:

EXAMINATION

BY MR. JENSEN:

Q. Good morning, Dr. Pyatt.
A. Good morning.
Q. My name is Steve Jensen. I introduced myself earlier. I represent the plaintiffs in this case.
You are a Ph.D. toxicologist. Is that correct?
A. That's correct.
Q. You do not have a medical degree. Is that right?
A. No.
Q. I'm sorry. Is it correct that you do not have a medical degree?
A. I do not have a medical degree.
Q. Okay, thank you.
Are you a colleague of Dr. Guzelian at the

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University of Colorado?
A. I know Phil. I've sat through a couple of meetings with him and we collaborated on a course at one point but it never came to fruition. So, I mean, I know who he is; he's at the university. But we're not really colleagues other than that.
Q. You didn't have any courses from him when you were in graduate school?
A. No. He came and gave a couple of seminars in our department through the years, but no courses.
Q. I am marking as Exhibit 1 a two-page document that is titled at the top Testimony Given By Dr. David Pyatt. And I would like you to confirm, Dr. Pyatt, that that is in fact a list of the testimony that you've provided in legal cases over the last four years.
A. This is right, but there are one or two other ones that have happened since I generated this list. So they would be like number 11 and number 12.
Q. All right. Can you remember the name of either or both of those cases?
A. Mm-hmm, I can. So number 11 would be Oakley.
Q. Oakley?

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A. Mm-hmm, versus Radiator Specialty and U.S. Steel. And then the last one was Thorpe versus Safety-Kleen.
Q. Thorpe versus Safety-Kleen. And do you recall in what jurisdiction the Oakley case is pending or was pending?
A. Yeah, it's over. Somewhere in Texas.
Q. Did you provide deposition or trial testimony or both?
A. Just deposition testimony.
Q. And it looks to me like the format that you have listed your appearances in Exhibit 1 lists the lawyer who took the deposition or who cross-examined you. Is that correct?
A. That seems to be the case, yes.
Q. And do you recall in the Oakley case who that lawyer was?
A. Lance Lubel.
Q. And in Thorpe versus Safety-Kleen, what jurisdiction is that case pending in?
A. I don't know the jurisdiction. It's in California.
Q. In California somewhere, all right.
A. Somewhere around L.A.; and it was Mr. Metzger, Rafael Metzger.

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Q. Are all of the twelve cases that are either listed on Exhibit 1 or that you've just described to me as a supplement to Exhibit 1 cases in which the plaintiff alleged that exposure to benzene or benzene-containing materials caused them to develop a disease?
A. Yes.
Q. If you could generally describe, what was the substance of your opinions in the Wilkerson versus Radiator Specialty case?
A. That's the first one?
Q. That's the first one. Denise Clancy is listed as counsel.
A. Right. Wilkerson, there was actually two plaintiffs but then they got separated and one went away, so Wilkerson was a non-Hodgkin's lymphoma case and it was alleged that solvents containing benzene were the cause of his disease.
Q. And the substance of your testimony was what?
A. The substance of my testimony was that the scientific literature does not support a link between benzene exposure and non-Hodgkin's lymphoma.
Q. So you provided what you understood to be a general causation opinion with respect to benzene

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and non-Hodgkin's lymphoma in Wilkerson. Is that correct?
A. That's correct.
Q. Has the substance of your opinions in all of the cases listed in Exhibit 1 been what you would describe as a general causation opinion?
A. Do you mind if I look at the list?
Q. Sure.
A. (Pause) I mean, I think that is part of it always. But, no, that's not always the only thing that I do. Some of these are not non-Hodgkin's lymphoma cases, and there you need to evaluate the dose-response relationship and whether or not the individual had opportunity for sufficient exposure to cause that disease. So that's a little different than just a straight sort of general causation argument. But many of these are.
Q. I understand.
So if I correctly interpreted your testimony, and I apologize for the width of the table making it difficult to pass the exhibit back and forth, but if I understand your testimony correctly, in certain of the cases listed on Exhibit 1 and also the additional two cases that you described, you provided testimony that -- Strike

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that. Let me try it again.
Some of the cases you provided general causation testimony only. Correct?
A. Yes.
Q. Some of the cases you've provided testimony that there was insufficient evidence to show that specifically this dose of benzene or benzene-containing materials could have caused the disease in this particular plaintiff. Correct?
MR. LEGHORN: Object to the form.
A. I think that's fair.
Q. Do you recall the disease at issue in the Remboldt case?
A. Remboldt? Yes. That was a non-Hodgkin's lymphoma.
Q. What about the Barker case in West Virginia?
A. Mm-hmm. Barker was an AML case. And Mr. Barker was a tanker driver, truck driver, and so the issue was the scientific literature around gasoline, as that is what he was exposed to.
Q. And what was the substance of your opinions in Barker?
A. Well, I'll have to give you a Cliff Notes version because I don't remember all the details.

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But that definitely the epidemiological literature dealing with gasoline exposure is sufficient to make a causal association with AML. That was part of it. But another part of it was that his disease was not consistent with our understanding of what a chemically induced AML will look like. The cytogenetics and some other morphologic aspects of his presentation was not what we would expect if it were really a chemically induced disease.
Q. You've finished your answer and I have no question pending yet.
A. Okay.
Q. Is it your opinion that a chemically induced acute myelogenous leukemia must necessarily have certain kinds of chromosomal markers?
MR. LEGHORN: Object to the form.
A. No.
Q. Describe for me what you look for to assess the extent to which a particular AML would or would not be caused by a chemical exposure?
A. Well, I think one clearly important aspect of that is the quantification of the chemical exposure you're referring to and what the scientific literature says about that chemical at any exposure. I'm assuming you're really asking about benzene or

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alkylating agents or I'm not sure what chemical you're referring to. Just in general? Because it's different.
Q. And that's fair. What I was really trying to ask and did so poorly was whether there are characteristics, biological characteristics, cytogenetics, anything else of a particular leukemia that you consider clues and/or necessary to be able to associate that disease with exposure to benzene or an alkylating agent, for example?
MR. LEGHORN: Object to the form.
A. I'll give it a try. I think I understand what you're asking.
Q. And if you -- Give it a try.
A. All right. There are clues, for sure. None of these are necessary. None of these are absolutely yes, it is, or no, it absolutely cannot be. There just seems to be too much variability in this area. But I think there are certain characteristics that have been repeated and observed repeatedly in cases to where you start to see patterns, and the discussion is: Is this presentation consistent with those patterns or is it inconsistent with those patterns? And those patterns being cytogenetics and morphology and

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pathology and response to treatment and other aspects, and it changes depending on the chemical, depending on the etiological risk factor.

For alkylating chemotherapeutic agents, I think the story is pretty clear. While there's always going to be some exceptions, you will frequently see a preceding myelodysplastic syndrome. You will often see cytogenetic, well, you will almost always see cytogenetic damage, so you're going to see some type of cytogenetic abnormalities. You will frequently see changes in chromosome 5 and/or chromosome 7. You will frequently see a hypocellular bone marrow and these individuals will be relatively refractory to any kind of therapy.

I think that where the appropriate analysis has been conducted, that seems to follow a pattern with a benzene-induced AML the closest, with the caveat that there are exceptions and there is variability.

Other classes of chemicals that have also been shown to cause secondary or chemically induced AML such as topoisomerase inhibitors, the presentation is quite different. And we can discuss that if you want. But it doesn't look the same as an alkylating-induced AML.

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Q. And just to make sure I understand, whether we're talking about alkylating-induced AML or we're talking about AML that has been induced by some agent that inhibits topoisomerase II, is it your testimony that while there are always clues and patterns to look for, that none of those characteristics that you're looking for would ever be a necessary agent to conclude without consideration of other factors whether that disease was linked to the exposure to either the alkylating agent or the topoisomerase inhibitor?

MR. LEGHORN: Object to the form.

A. I think if you don't have information about the exposure and you're just presented with a case of AML and asked to deduce what caused it, then the answer to that is probably -- I mean, I think the answer to your question is yes. There isn't going to be a blueprint that anyone can follow and say absolutely, this is a chemically induced disease.

If you're following a patient in the clinic and they receive seven rounds of cyclophosphamide and four years later they develop AML and it has a monosomy 7 and 5q deletion, I think it's a pretty straight line to say this is

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definitively caused by that exposure. So it really just depends on the circumstances.

Q. And I was trying to really ask about the flip side of the example or the hypothetical you're talking about, rather than suggesting that any one of these characteristics might lead you to necessarily conclude that this is definitely a chemically-related disease. I was asking whether it is your opinion that the absence of any given characteristic or set of characteristics can lead one to conclude that the disease is not related to chemical exposure.

MR. LEGHORN: Object to the form.

A. I don't think you can do that with a hundred percent certainty. With the example that I just gave, if someone did receive alkylating chemotherapy and then four years later, five years later they developed AML but there were no cytogenetic changes, that would be a puzzle. And there are very good, well-published researchers who have suggested such an event might not be related to the chemotherapy and that it was just an event that happened, because it is so inconsistent with our understanding.

So, again, it's not absolute, not a

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hundred percent, so the word "necessary" in your question would probably mean the answer would be no. But it is more a matter of does it fit with our understanding and the scientific picture of what these diseases would look like. And if you don't see these changes and other characteristics are inconsistent, then you have to weigh that into consideration and say it doesn't look like this is a chemically induced disease.

Q. What are the characteristics of a leukemia that has been caused by topoisomerase inhibition?

MR. LEGHORN: Object to the form.

A. Without trying to be cute, you actually have to identify more carefully what type of topoisomerase inhibitor you're referring to, because as we move further into this and understand what these diseases look like, we're starting to see that you actually get different presentations following different kinds of topoisomerase-reactive drugs or inhibitors.

In general, as a general rule, it's going to be AML and it is most frequently going to have a cytogenetic change or a translocation on the 11th chromosome, 11q23, which involves the MLL gene, and it will have a variety of translocation partners,

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some of which are thought to play a role in the disease. Some we're not so sure. There is most often not a preceding myelodysplastic syndrome. The latency is quite short, sometimes as short as six months to a year; two years or three years and it's going to happen if it's going to.

They will appear to be as treatable as a de novo leukemia, so there doesn't appear to be any big difference in their response to treatment. And there is not as frequently a hypocellular marrow, so you don't necessarily see the kind of damage in the bone marrow that you see following alkylating therapy. That's in general for a topo-reactive drug.

Q. Is it your opinion that the scientific evidence is sufficient to conclude more likely than not that topo-reactive drugs cause APL?

MR. LEGHORN: Object to the form.

A. Etoposide, which really would fall into the category that I just described and that is the prototypical topoisomerase inhibitor, rarely causes APL. You can find scattered reports here and there, but by and large the answer to that is no, you don't see them. And it is so rare, perhaps it's not even related. But there are other kinds of topoisomerase

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inhibitors and that's what I was getting to earlier. One is a Chinese drug called bimolane and then there's a derivative of that that they isolated from that, I think it's a root, but whatever, and that is thought to also inhibit topoisomerase II. It's not known if that's what makes it leukemogenic but that also does it. And in that case of bimolane you do see an increase in APL, so there are some types of drugs that can inhibit that enzyme that do seem to be associated with APL.

Q. Is it your view that besides bimolane and its derivatives you just described the scientific evidence is insufficient to assess whether any other topoisomerase inhibitors cause APL?

A. No, that's not my testimony. I was giving you examples of where it did happen and where I thought it didn't happen. There are lots of other topoisomerase inhibitors that we haven't discussed.

Q. And do some of those topoisomerase inhibitors cause APL?

MR. LEGHORN: Object to form.

A. There's mitroxantrone, which is another that is thought to act in a manner comparable to bimolane, and in some individuals who are treated with that drug there's a secondary leukemia that is

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APL.

Q. The scientific literature as you understand it with respect to how these different kinds of topoisomerase inhibitors act on the body, does it provide strong evidence as to why certain of them seem to cause APL more often than others?

MR. LEGHORN: Object to the form.

A. That's a good question. We start by saying that there is also a variety of chemicals that have been shown to inhibitor this enzyme, topoisomerase II, that aren't leukemogenic at all. So it isn't a foregone conclusion in a straight line that if a drug or chemical inhibits this enzyme, that it is in fact going to cause any kind of leukemia, because there's plenty of examples where that's not true.

To answer your question why do these increase the risk of APL and others do not, it is certainly not known with any kind of certainty. There have been suggestions of ethnic differences, because bimolane was predominantly a Chinese traditional medicine. Maybe it has something to do with the background genetics of the population. But the short answer is no, there's not a definitive explanation for why that's true.

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Q. Am I correct, Dr. Pyatt, that your report does not specifically discuss or describe the opinion that you just gave that certain topoisomerase inhibitors do not cause leukemia?

A. I'd have to go back and look. I don't think I explicitly put it in my report. That is common knowledge and it is certainly in all of the references that are in my report, but I'm not sure that I explicitly said what I just said to you.

Q. Can you give me examples of chemical agents that meet that criteria?

MR. LEGHORN: Object to form.

A. There's tons of them. Genistein, which is a chemical that you can isolate from soy products, is a topoisomerase inhibitor. And in fact they think that might be why Asian women have a lower incidence of breast cancer, because they have a higher intake of soy, they have a higher intake of genistein, but it does inhibit that enzyme. Ciprofloxacin inhibits the enzyme. It's not leukemogenic, or there is certainly no evidence to support it, as well as other quinolone antibiotics.

There's many, many, many chemicals that will inhibit this enzyme. Really, like I said, it's common knowledge within the topoisomerase business.

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That's probably why I didn't put it in there.
Q. And it is fair to say that the scientific evidence that has been developed to date doesn't show why some topoisomerase inhibitors cause leukemia and others do not. Is that true?
A. It's true up to a point. I mean, we're not totally sitting around in an informational vacuum. We know a lot about these drugs and we know a lot about how they behave and we think that a chemical's ability to stabilize what are called cleavable complexes is thought to be an important part of its ability to result in translocations, which then in turn may result in leukemia. But there is certainly more to the story than what we know right now and we don't have all those answers.
Q. Do you agree that benzene is a topoisomerase inhibitor?
A. No.
Q. Do you agree that any of benzene's metabolites are topoisomerase inhibitors?
A. That's a better question. I think you have to define the -- I'm sorry. I wasn't trying to be sarcastic.
Q. I understand.
MR. MILLER: He appreciates the

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compliment, especially after yesterday.
A. I'm sorry. Could you ask your question again?
Q. Sure. I asked whether you agreed that any of benzene's metabolites are topoisomerase inhibitors.
A. Yes. Under very carefully controlled and defined experimental conditions, you can see in vitro inhibition of that enzyme. Now, does that translate even into a cell or an animal or a human? That is not known. But in a test tube, under clearly defined experimental conditions that if they vary very much then the answer is maybe not, but under those conditions, yes, some of benzene's metabolites can inhibit this enzyme.
Q. Has there been published research in the peer-reviewed literature looking at the extent to which any of benzene's metabolites inhibit that enzyme in vivo?
A. In an animal in vivo? The only data that I have ever found, and I wouldn't say that it was published in the peer-reviewed literature, it was a published report that Dr. David Eastmond wrote. He did some in vivo experiments with various metabolites and reported his data, but it wasn't in

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the peer-reviewed literature. So if that's the criteria, I guess the answer is no, there is no data, that I'm aware of.
Q. And what did Dr. Eastmond's report indicate?
A. As best I recall, what he reported was in really, really highly exposed animals that he saw a 38, I think a 38 percent decrease in the activity of the enzyme in the bone marrow of these mice that he exposed. That's what I recall.
Q. Are there any studies that have looked to whether benzene-exposed workers have topoisomerase inhibition?
A. There are no studies per se looking at the activity of the enzyme before and after benzene exposure in workers. But there is at least one study that Dr. Smith published where they did look for 11q23, which is far and away the most common cytogenetic change that you would associate with topoisomerase inhibition, and he did look for that in benzene workers and he did not see it.
So while he didn't look specifically for enzymatic activity, that cytogenetic change would be consistent with it occurring. The lack of that cytogenetic change is inconsistent with it

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occurring.
Q. Which paper is that that you just referred to by Dr. Smith?
A. Oh, I'd have to go back and look. I'm sure I referenced it. He looked for 11q23 with two of the three most common translocation partners. Let me just look at my report, see if I can find it there. (Pause) I'm looking. Sorry.
Q. That's okay, Doctor.
A. I don't think he was the first author.
MS. SHEEHAN: Excuse me. While the doctor is looking for that, could you fix the LiveNote?
MR. LEGHORN: Yes, we can.
THE WITNESS: I'm sorry, Steve. I know it's in here somewhere. I'll find it.
MR. LEGHORN: Hold on. We're taking a little break.
(In recess 9:39 a.m. to 9:42 a.m.)
BY MR. JENSEN:
Q. You were looking for the reference to the Smith article.
A. Right. It was 2007 and I did reference it in my report, but I didn't reference it correctly, because 46, if you have my report --
Q. I do. I was looking for it.

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A. It's going to be saying 2007, and on page -- they're not numbered. Well, look on paragraph 18, where it starts with "11q23, which is the most common cytogenetic abnormality, has also not been seen elevated in benzene-exposed workers or in leukemia patients with a past history of excessive," and that should be the Zhang 2007 paper, not the Lovett one, the one that I mistakenly have referenced in here. So that's why I don't have it. I knew I had referenced it.

Q. And just so I'm certain we're talking about the same thing, Zhang is Z-h-a-n-g. Correct?

A. Yes.

Q. And the paper is Aberrations in Chromosomes Associated with Lymphoma and Therapy-Related Leukemia in Benzene-Exposed Workers. Is that right?

A. That's correct. And I have an electronic version right here on the computer, if you want to discuss it. Thank you, Joe. Yes, that is the one.

Q. And am I correct that other than that paper, the Zhang et al. paper, you're not aware of any other scientific literature in which the issue is whether benzene-exposed workers have shown characteristics of topoisomerase inhibition. Is

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that true?

A. Other than that paper -- What was the question? I am not aware of any other scientific -- ?

Q. Literature in which the investigators have tried to assess the extent to which benzene-exposed workers are showing characteristics of topoisomerase inhibition.

A. Okay.

MR. LEGHORN: Object to the form.

A. Yeah, there are no studies where they have actually looked at the enzyme and tried to evaluate whether or not there are changes in vivo in the enzyme. But there are many studies where they have looked at cytogenetic abnormalities associated with benzene-exposed workers. This one explicitly looked at 11q23 and didn't see it, but others have not reported that finding either and, really, the issue today about APL and 15;17, that evidence has something to bear on this as well because of the bimolane connection and that some drugs that inhibit the enzyme can cause that disease.

So if they have ever looked for 15;17, I would say that has bearing on this question as well.

Q. What studies besides the Zhang 2007 study

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are you aware of in which the investigators looked for the 15;17 translocation in benzene-exposed workers?

A. The only one that I know specifically is the McHale paper which was published in 2008, also co-authored by Dr. Smith, and in that case they did not see an increase in 15;17 in the exposed workers.

Q. Is reference 22 in your report the Eastmond report that you described earlier in your testimony this morning?

A. Yes. And I think that data was presented by one of his co-authors, who I can't remember, in a book chapter or a proceeding or something, because there seemed to be two references but neither one of them was in the peer-reviewed literature. This is the one that I was talking about, yes. It's the same data; I think it's just been presented twice in this form.

Q. Is it your view that any scientist who looks at the available evidence regarding benzene and its metabolites and their ability to cause topoisomerase inhibition and concludes from that available evidence that benzene's metabolites do in fact cause topoisomerase inhibition in people is being unreasonable?

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MR. LEGHORN: Object to the form.

A. I don't know what you mean by unreasonable. I think anyone who looks at that data and looks at the work that David Eastmond did, that Rhonda Baker did with me and Rich Irons and that Neil Osheroff has done would recognize that the experimental conditions are critical for observing inhibition. To look at that and say, yeah, absolutely it's going to happen in humans, I don't know if it's unreasonable, but I think it's premature and I think it is making a leap of faith that the science doesn't support without understanding which of the experimental conditions most likely mimic what you're going to find in the bone marrow and whether it is possible for anyone to even survive the exposures to benzene that would allow those concentrations to get into the bone marrow to cause those changes.

So those are two really big questions right now that are unanswered. So I don't know that it would be unreasonable, but I think it's a reach.

Q. You know Dr. Martyn Smith. Isn't that true?

A. Yes.

Q. Would you agree that he is one of the most

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highly published researchers in the area of benzene toxicology?
MR. LEGHORN: Object to the form.
A. Dr. Smith has published on certain aspects of benzene toxicology quite a bit, yes.
Q. And he has published a lot more papers that relate to benzene toxicology than you have, for example. Is that true?
A. I would say that's probably true.
Q. And would you agree that Dr. Smith's reputation in the field of benzene toxicology is that he is considered a highly respected scientist in that area?
A. I think Dr. Smith is considered, and I consider him, to be a respectable scientist, yes.
Q. And specifically with regard to benzene toxicology. Is that true?
A. Specifically with regard to certain aspects of benzene toxicology, Martyn -- Dr. Smith -- has published a lot on cytogenetic changes associated with benzene exposure. There are other areas that he has not published as much on, but that one area I'd say he probably is in the lead at this point.
Q. Bear with me just a moment, Doctor.

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(Pause)
It appears I've made a silly mistake in two respects, one being I only brought a single copy of something I wanted to look at and the other being I think I marked it as an exhibit yesterday. But I bet you have a copy in front of you. I was looking for the supplemental declaration of Dr. Smith in this case.
A. I do have it.
Q. Okay. And you've read that. Correct?
A. I have.
Q. Have you reached some opinions in this case since reading Dr. Smith's supplemental report that are not reflected in your original report in this case?
A. Well, I think all of my main opinions are reflected in my original report, but I have many opinions related to Dr. Smith's supplemental report that are not covered in my original report.
Q. I want to ask you specifically about a discussion in Dr. Smith's supplemental report regarding the extent to which leukemias as a group develop from a common stem cell. Do you recall the discuss I'm talking about?
A. Yes, mm-hmm.

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Q. You have in your original report a reference that you say shows that Dr. Smith's original report, as I recall, that statements in Dr. Smith's original report regarding that are incorrect and then Dr. Smith, as I recall in the supplemental report, responds to your reference. So I'm here to ask you: What is your response to his response or your reply to his response?
A. Yeah, Dr. Smith pointed out that the Jandl reference was outdated. I don't know that that's true or not. I mean, it's still an excellent hematology textbook, but it was published in '96 or '97. Then he points out sort of this evolving notion of the leukemic stem cells, which is clearly important, particularly from a therapeutic point of view, and may have some bearing on the cell of origin. But I'm not sure that it necessarily does.
My position that these different types of leukemias, particularly of the form of AML that is a quite differentiated cell type like an acute promyelocytic leukemia, are not likely to have arisen from the same stem or progenitor cell that something like chronic lymphocytic leukemia would arise from; and I still believe the scientific data support that. This would be one area that I think

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perhaps it's just a disagreement and Dr. Smith and I would not see eye to eye on what the data says or from a conceptual point of view.
Because the bottom line is, we don't know. We just don't know where these various forms of leukemia arise, in what cells. But if you look at the presentation of the disease with the cytogenetic changes, it seems pretty clear to me that they are not all arising from the same cell. And the World Health Organization has a hematopoietic classification system and document that they published in 2004; and their statement, while it's cursory, would support my position that these diseases do not all arise from the same level of hematopoietic organization.
So some of the things that he suggested that I was wrong on, perhaps he's correct. But the overriding principle that these diseases do not come from the same source cell I still believe is supported by the scientific evidence.
Q. And when you say these diseases, you're talking about leukemias as a group. Correct?
A. I'm talking about, yes, leukemias as a group, chronic versus acute, lymphocytic versus myeloid, and potentially even the various forms of

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acute myelogenous leukemia may not arise in the same cell.
Q. Do you have an opinion one way or the other to a reasonable degree of scientific certainty as to whether the different variants of acute myeloid leukemia do arise from the same progenitor cell?
MR. LEGHORN: Object to the form.
A. I would say that it is a matter of speculation. But if you look at the presentation, I think the evidence would argue that they probably do not arise from the same cell. But they could. But I clearly believe that whatever that cell is, however undifferentiated the cell of origin for any form of AML is, it is a different cell than the cell of origin for chronic lymphocytic leukemia or even chronic myeloid leukemia.
Q. With respect to the last question that I just asked you, about the different subvariants of AML and the extent to which they arise from the same progenitor cell, is that issue something that you would say reasonable scientists could disagree about?
MR. LEGHORN: Object to the form.
A. Reasonable scientists do disagree. If you

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go to an experimental hematology meeting, those guys will get in a fistfight over this issue. I mean, it is not clear. We can't tell what cell is doing what. So, yes, the answer to your question is clearly there are many disagreements about this particular issue. And I was exaggerating about the fistfight.
Q. I wouldn't ask you to name names even if you weren't.
A. But strongly worded arguments occur at every experimental hematology meeting that I've ever been to.
Q. Is there scientific consensus that acute myeloid leukemias develop in a multistage fashion?
MR. LEGHORN: Object to form.
A. Is there scientific consensus? Is that what you asked?
Q. That's what I asked.
A. I think that is a theory. I think that there are hypotheses and there's data that support that. I don't know whether it's a scientific consensus or not, but I think most scientists think about all cancers as being a multistep process.
Q. And part of that theory is that the process at least with respect to AMLs begins at a

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progenitor cell. Correct?
MR. LEGHORN: Object to the form.
A. Well, it starts getting semantical when you use the word progenitor cell. What exactly do you mean by a progenitor cell?
Q. I see your problem. (Pause) Let me ask a different question that goes to a similar issue.
A. Okay.
Q. I'm looking at Dr. Smith's original declaration --
A. Okay.
Q. -- and I'm at paragraph 28(a). The second sentence of paragraph 28(a) says "Since the subtypes of AML all derive from a genetically damaged pluripotent stem or progenitor cell, they likely have a common pathogenesis." My first question for you about that sentence is: Do you agree with Dr. Smith that the subtypes of AML all derive from a genetically damaged pluripotent stem or progenitor cell?
A. Well, again, it's semantical. I mean, by the word "or," is he saying that a pluripotential stem or progenitor cell are interchangeable with one another? In my view as an experimental hematologist in the lab, that's not the case. Those are very

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different things. A progenitor cell is not a pluripotential stem cell. Those are different. So if he's saying can it arise in this animal or this animal, I think the answer is yes, as long as we understand that those two animals are very different. If he's saying that all forms of leukemia arise in one of those animals as opposed to the other, I think that's speculation.
Q. What is a progenitor cell the way that you've used that term?
A. A progenitor cell is one that has lost the ability to differentiate into some types of lineages, cell lineages, but is not terminally differentiated so it still has the ability to turn into more than one kind of cell. And it stays that until it becomes a lineage-committed progenitor cell and then it's irrevocably committed. Well, I wouldn't say that, because now there's some plasticity, but it is heading down a path of becoming a red blood cell or a neutrophil or whatever it's going to be. A pluripotential stem cell is at the very top. It has retained all of the hematopoietic capacity that exists and it can turn into whatever physiologically it needs to turn into.
Q. And I apologize, Doctor, if you answered

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this earlier but I don't think that you did.
A. It's all right.
Q. No, and I'm not sure I asked this specific question either so I'm not trying to criticize you.
Is it your opinion that APL arises from a different progenitor cell than other forms of AML?
A. That wouldn't surprise me. And I think you can certainly make a cogent argument why that would be the case, but I would allow that there are other alternatives and that they could be coming from potentially the same, as long as we're talking about acute myeloid leukemia, AML, not other forms.
Q. Is there evidence that benzene or its metabolites are causing damage at the progenitor cell level that is ultimately one of the factors that is leading to AML developing in benzene-exposed people?
MR. LEGHORN: Object to the form.
A. I think I heard the whole question, but I'll just answer it and if it's not right, you can follow up.
The progenitor cell, hematopoietic progenitor cell population is a target tissue for benzene toxicity. Now, whether those changes ultimately result in leukemogenesis, well, I think

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some of them might but we certainly can't clearly identify what those pathways are at this point.
Q. To the extent that benzene causes damage at a progenitor cell level that ultimately leads to leukemia, if you would just assume that for me for the moment. Okay? And if you also would assume that the progenitor cell in which APL arises is the same progenitor cell in which the other forms of AML arise. Okay? Given those two assumptions, is that some evidence in your view that benzene is capable of causing APL?
MR. LEGHORN: Object to the form.
A. When you first started that question you said leukemia. And by leukemia, you're talking about AML, not all leukemias?
Q. Yes. Let's put that in the question, if I didn't say that.
A. All right. Because I would take issue over that. But if you talk about acute myeloid leukemia and then the second part of this hypothesis was that all of the different subtypes of AML arise from the same progenitor cell?
Q. Correct.
A. Is that evidence that benzene can cause all those different forms?

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Q. Is that evidence that benzene can cause acute promyelocytic leukemia?
A. Okay. If that were all there were to the story and that's all we knew and that's the only piece of data on this table, sure. I don't think there'd be any reason to argue that one form or another is not likely to be caused by benzene. In this particular instance that is not all there is on the table. We have a lot of other evidence dealing with this very question of whether benzene is related to APL, and that does not support that hypothesis. But just based on your question and that piece of data, yes.
Q. Would you agree that the body of epidemiological literature regarding benzene exposure and the acute nonlymphocytic leukemia shows a strong association?
MR. LEGHORN: Object to the form.
A. I think the body of epidemiological literature at somewhere greater than 50 part-per-million-years benzene within an appropriate window of opportunity or latency or exposure window, however you want to put it, that supports strongly a link with some forms of acute nonlymphocytic leukemia.

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Q. You would agree with me that most of the epidemiological studies that have looked at the issue of benzene exposure and acute nonlymphocytic leukemia have not attempted to sort out by subvariant which types of ANLL are occurring in the benzene-exposed populations. Right?
A. Well, define "most." I mean, some?
Q. More than half.
A. Yes, yes, most of them have not, based on that, tried to distinguish the various subtypes. And if they are retrospective mortality studies, that's really hard to do.
Q. Are you aware of any cohort epidemiology studies that have attempted to calculate a relative risk or other measure of association between benzene exposure and APL specifically?
A. Quantify the risk, SMR or odds ratio or something like that?
Q. Correct.
A. And benzene?
Q. Correct.
A. Identified benzene with quantitative exposure information for that benzene?
Q. Quantified, or qualitative benzene exposure information, either one. Are you aware of

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any cohort studies that have attempted to do that?
A. Not yet.
Q. Are you aware of case-control studies looking at APL in which benzene exposure specifically was analyzed for an odds ratio?
A. With APL?
Q. With APL.
A. Benzene exposure specifically, no.
Q. Would you agree that there are many case-control studies that have looked at acute nonlymphocytic leukemias as a group and analyzed for an odds ratio for benzene specifically?
MR. LEGHORN: Object to the form.
A. Yes, there are studies that fit that criteria, yes.
Q. And those studies are part of the body of literature that we were just discussing with respect to showing an association between benzene and AML or ANLL. Correct?
A. Yes.
Q. And just to finish my line of questioning about that body of literature generally, would you agree that that body of literature shows a consistent association between benzene exposure and ANLL?

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MR. LEGHORN: Object to the form.
A. With the caveats that I put into my first answer, you see a consistent association under appropriate exposure conditions.
Q. And would you agree that that body of literature shows that there is a dose-response connection between benzene exposure and ANLL?
A. Yes.
Q. Would you agree that there is a scientific consensus that benzene exposure is capable of causing ANLL?
MR. LEGHORN: Object to the form.
A. Under the appropriate exposure conditions.
MR. JENSEN: Let's take a short break.
(In recess 10:16 a.m. to 10:27 a.m.)
BY MR. JENSEN:
Q. Dr. Pyatt, the list of testimony that is Exhibit 1, is it true that in each one of those cases you provided testimony at the request of defense attorneys in the case? Is that right?
A. That is correct, yes.
Q. Had you provided testimony in legal cases in years preceding the years that are represented by Exhibit 1?
A. No, that's it. That's my sum total.

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Q. Okay. So is it fair to say you have never provided testimony at the request of or on behalf of a plaintiff in a personal-injury case?
A. Not yet.
Q. If you would turn with me back to the original declaration of Martyn Smith for a moment, at paragraph 24. The first sentence of paragraph 24 says "The rarity of APL makes it difficult to study by traditional epidemiological methods." Do you agree with that?
MR. LEGHORN: Object to the form.
A. APL is a relatively rare disease. I mean, AML is a relatively rare disease and this makes up some portion of those. Whether or not it's difficult to study with traditional epidemiological methods, you would have to ask an epidemiologist that question. I think it can certainly be done and has been done.
Q. Am I correct that in your view the most important body of data to examine when looking at an issue of general causation with respect to a particular substance, exposure to a particular substance and a particular disease, is epidemiological literature?
A. The most important? I would say that's

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the most important, yes. I would say that's not all you should look at. You should look at every bit of scientific data you can find. But, yes, I think that's the trump card.
Q. I have in front of me an article entitled Mechanism of Action of Eukaryotic Topoisomerase II and Drugs Targeted to the Enzyme by Burton and Osheroff in 1998. You are familiar with that article?
A. Yes.
Q. I believe that this article was recently identified by counsel yesterday as being something that you were relying on. Am I correct that you did not list this particular paper as a reference in your original report?
A. This is not listed in my original report, no.
Q. For what purpose are you relying on the Osheroff 1998 paper?
A. I brought this study because it explicitly, but it wasn't the only one, there were other references in my report that talked about these other drugs that inhibit this enzyme that are not leukemogenic. And Mr. Leghorn thought that you would want a copy of it since it was not listed in

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the report per se.
Q. Which portion of the Osheroff paper or Burton paper discusses topoisomerase inhibitors that are not leukemogenic?
A. Well, if you look on page 145, these are representatives of various types of drugs that are known to inhibit this enzyme. Genistein, there's no evidence that genistein is leukemogenic, so I don't know that it specifically says that in this paper, but it's in the scientific literature. There's no evidence that it is, so you just put two and two together.
The reason why these structures are put here -- and it's really kind of how people came about thinking that benzene might be going through this mechanism -- are some of the structural similarities in the metabolites or these compounds and what we see from the benzene metabolites. That's how this whole discussion kind of came about.
Q. Are you aware of any studies that have looked to the specific issue of whether genistein is capable of causing leukemia?
A. Well, the flip side of that question is there is no evidence that it does, ever, in any study that I've ever seen.

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Q. And I'm just asking whether you've seen a study that specifically was asking that question.
A. And I think the answer to that is no.
Q. With respect to any of the drugs which are topoisomerase inhibitors but for which there is no evidence in your view that those particular drugs cause leukemia, are you aware of any epidemiological studies that have looked to the specific question of whether drug X, which is a topo inhibitor, causes leukemia?
A. I think those studies exist. Not that they went after and specifically looked for leukemia, but in the clinical trials for ciprofloxacin and for some of these other antibiotics, there's all kinds of clinical data on the use of these drugs, and that would turn up. And there may very well be long-term studies out there that have cancer incidence rates; I just can't identify them sitting here right now.
Q. Are you aware of any epidemiological studies that calculate a relative risk, an SMR, an odds ratio, or any other statistical measure of association with respect to benzene exposure and any of the specific subtypes of AML?
A. Not yet.

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Q. Is it your view that the weight of the scientific evidence is that benzene exposure is capable under certain exposure conditions, as you've described it, of causing all forms of ANLL other than APL?
MR. LEGHORN: Object to the form.
A. That's fair. The only one that I think would be questionable would be perhaps M7, the megakaryocytic leukemia, just because it is so exceedingly rare, you just don't have any real data on it one way or the other. But there aren't any other forms based on the FAB subtyping that I would at this point call into question. The only reason why you can identify APL and call into question APL is because it is unique enough where people have isolated it, talked about it, and have done separate epidemiological studies on that specific subtype. That has not been done with any other subtype that I'm aware of.
Q. But, again, the separate epidemiological studies that have been done with respect to APL as a specific subtype, as far as you're aware, none of those have attempted to quantify a statistical association between APL and benzene exposure specifically. Right?

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MR. LEGHORN: Object to the form.
A. I would have to look at some of Dan Douer's studies, but he clearly stated that there were no environmental or occupational risk factors for APL. I don't recall sitting here whether he specifically went in and looked quantitatively at benzene. But I think anyone going in and thinking about APL as a separate disease entity would have in the back of their mind benzene. So, I mean, I'm sure that was part of his thought process.
Q. As you sit here today you can't point to any such study by -- Is it Douer?
A. Douer.
Q. -- or any other investigator. Is that correct?
A. That have quantitated the relationship between APL and benzene statistically? No.
Q. Are you aware of any studies that have attempted to quantify a statistical association between APL and solvent exposure?
A. I'm not.
Q. Are you aware of any studies that have attempted to quantify a statistical association between APL and petrochemical exposure?
A. No, not as I'm sitting here right now.

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Q. In fact, is it fair to say, Dr. Pyatt, that to date the epidemiological investigations of benzene exposure and ANLL have not even attempted to investigate a relationship by subtype of those ANLLs?
MR. LEGHORN: Object to the form.
A. No, I don't agree with that. I don't think that is fair to say.
Q. Okay. Why do you think that's not fair to say?
A. Well, because your sole criterion that you've been posing all these questions is, is there a statistical relationship? Has someone gone after the quantification? And I think the answer to that part is no. But they have listed the subtypes and have gone after certain cytogenetic changes in a variety of studies and they don't see any APLs or they see one APL. And if you have one APL in the exposed and a variety of them in the unexposed, you can't do statistics. There's not a way to rationally do that.
So I think your question is too narrow with regard to the quantification. But I think there is evidence addressing the overriding question of whether benzene is associated with this disease.

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Q. And is all of the epidemiological evidence that you just referred to in your last answer referred to in your original report in this case?
A. Yes.
Q. If you would turn with me to your report at paragraph 18.
A. Okay.
Q. For context I will read the first sentence. The first sentence says "The relevance that topoisomerase inhibitor-induced AML has to the issue at hand relates to reports that benzene metabolites can inhibit topoisomerase II, which in turn has been hypothesized to be a potential mode of action for benzene's cytogenetic effects and leukemogenic effects. However, this picture is far from clear and other published work has shown that the mechanism of inhibition of topoisomerase II by benzene metabolites may be inconsistent with this hypothesis and, further, that benzene metabolites might actually protect cells from etoposide-induced DNA damage." And then it gives reference number 7, and reference number 7 is the Baker paper that you alluded to earlier in your testimony this morning. Correct?
A. Yes.

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Q. And you were one of the co-authors on that paper. Right?
A. Correct.
Q. Besides the Baker paper, can you identify any other studies in the literature that support the proposition that benzene metabolites might actually protect cells from etoposide-induced DNA damage?
A. I'm not sure that anyone's ever looked at that other than us. I think Rob Schneider's paper, which maybe is reference 28, where he looked at these issues in whole cells -- yeah, 28 -- that is 32.D3(G) cells, it's a bone marrow cell line, he found that at doses of parabenzoquinone that started inhibiting the enzyme, the cells died; that they underwent apoptosis. That is also a mechanism that in my view would be inconsistent with a leukemogenic process.
Q. Are you aware of anyone replicating Dr. Schneider's results with respect to that issue?
A. I don't think anyone has used those cell lines. But if you understand how the enzyme works and the cell's requirement for that enzyme, that's not very far out on a limb that the cell will die if you inhibit this enzyme. So, A, I don't think it was really an earth-shattering study that it needs

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to be repeated. I think that data speaks for itself and it's pretty consistent.
Q. Well, when you say it's consistent, can you point to any other publication that provides evidence of that specific point that topoisomerase inhibition by benzene metabolites kills hematopoietic progenitor cells other than reference number 28?
A. Well, sure. That's how it works. Any paper that explains the mechanism of topoisomerase inhibition in the diseases that are being treated for, it's killing the cells. That's why it's a chemotherapeutic agent. It kills the cells because it increases the amount of these cleavable complexes and the cell dies. The cell doesn't want to have all of that damage and it goes through apoptosis. That's how this drug works. That's its mechanism of action. So there's hundreds of studies, probably, that would support that position.
Q. Well, isn't it true that in the instances in which topoisomerase inhibitors end up causing a therapy-related leukemia, some of the cells have not been killed by the drug. Right?
MR. LEGHORN: Object to the form. Go ahead.

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A. There has to be a fine line in there somewhere and we don't understand exactly how that works. But that doesn't change the fact that that is the mechanism of action for these drugs. If it didn't kill these hematopoietic cells, it wouldn't be very useful in treating leukemias or in treating lymphomas or these other things that it's used for.
Q. So clearly the drugs that are topoisomerase inhibitors are not always killing all the cells in which they are causing the DNA cleavage. Right?
MR. LEGHORN: Object to the form.
A. Clearly the drugs are not killing all the cells in which they are causing DNA cleavage? Well, some of the drugs probably doesn't necessarily even cause DNA cleavage. But the ones that have been established to be leukemogenic, like etoposide for example, it's thought to be some repair mechanism that has gone awry where it has cleaved the DNA and borne these cleavable complexes but in the process of repairing that break in the DNA, something hasn't worked correctly and that has allowed that cell to survive. And if that repair mechanism confers on that cell a growth advantage or some dysregulation, then that is in the most simple terms how it could

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potentially become leukemogenic.
Q. In your view, does Dr. Schneider's work referenced in number 28 in your report demonstrate that benzene metabolites cannot work with the same repair mechanism that you just described with respect to drugs which are topoisomerase inhibitors? Does it exclude that possibility?
MR. LEGHORN: Object to the form.
A. I don't think it excludes that possibility. It's a transformed cell line out of a mouse bone marrow. So, I mean, you've got to put it all into context. But I think it is inconsistent with that mechanism and I think it is data that you would put on the other side of this debate as to whether or not the inhibition that you can sometimes see with benzene metabolites is a relevant mechanism for benzene to produce leukemia.
Q. If you would turn to paragraph 15 of your report.
A. Okay.
Q. You're discussing there the -- I'm not sure whether it's Melay or Melie. In Italian it would be some form of Mele.
A. That's the way I say it, something like Pele.

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Q. The Mele study. And this was a case-control study of APL. Correct?
A. A very small one, yes.
Q. And the case-control study found a statistically significant odds ratio with respect to shoe workers in Italy and incidence of APL. Correct?
A. Well, that is what they reported. But I take issue over that statistical analysis they did because they're working with two cases. I mean, they report a relative risk of 6 or something, but there's only two cases. That just, to me, is inappropriate.
Q. Well, they also calculate a confidence interval around the odds ratio. Correct?
A. That doesn't change the fact that all of that math and that statistics is based on an extremely small number of cases, two.
Q. And I understand your opinion in that regard, Dr. Pyatt. But there are, you would agree, conventions in epidemiological literature and in biostatistics in general for determining whether or not a particular result is statistically significant. Right?
A. The answer to your question is yes, of

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course there are. The caveat is whether or not this fulfilled that statistical requirement, I don't know the answer to. In my line of work an N of two is not a sufficiently robust sample size to run any kind of statistics on, ever.
Q. Well, at least if the authors report the confidence interval, this finding meets the conventional definition of statistical significance as you understand it. Am I right?
A. Based on what they reported, sure, yes.
Q. Now, in your report at paragraph 15 you say in the middle of that paragraph "In fact, due to the timing of exposure with these workers, it is unlikely that they were using benzene in their adhesives at all, as it had been banned by the Italian government for such purposes in the 1970s." What is your authority for that proposition?
A. My authority?
Q. What you are relying on for the proposition that the Italian government banned the use of benzene in the '70s.
A. Oh. Actually, as I recall now, it was in 1965, so it was actually earlier than the 1970s. It seemed like, and I don't know this a hundred percent, but that it was a review paper that Aksoy

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published where he was talking about some European cohorts and how the regulations have changed through time with regard to benzene. But I'm not positive if that's the one.
Q. Would you agree that based on the language of the Mele article itself, it appears that the author believes that the shoe workers who were part of his study were in fact exposed to benzene?
MR. LEGHORN: Object to the form.
A. No, I wouldn't agree with that. I don't know what these authors thought.
Q. You don't think that the language suggests that?
MR. LEGHORN: Object to the form.
BY MR. JENSEN:
Q. That's not your interpretation of the language. Correct?
A. That the language suggests that the shoe workers were exposed to benzene?
Q. Suggests that the authors believed that the shoe workers were exposed to benzene. I understand you've got a separate opinion which you've made in this report about that. I am just asking you about whether the language suggests that the authors' opinion was that the shoe workers were

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probably exposed to benzene.
MR. LEGHORN: Object to the form.
A. I have it right here. Just give me one second and I'll read what they say. (Pause) Okay. So what was your question again? Does the language suggest that these authors thought that the workers were exposed to benzene in the glues?
Q. Yes.
A. I don't know. I don't know how to answer that. What they say is "A significant relationship between shoemaking and APL is possibly related to benzene exposure, a well-known leukemogenic agent present in the glues." I don't know if they're talking about their glues. They're not referring to -- They're talking about old studies where benzene was in the glues. I don't know what they thought.
Q. Is it true you can't point me to a specific Italian regulation or law that banned use of benzene in adhesives?
A. I can't sitting here. But the next time we get together I'll be able to.
Q. Well, can you tell me as we sit here today how the Italian government enforced any such regulation?

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A. No.
Q. And you can't tell me as we sit here today the extent to which any compliance efforts with such a regulation were effective. Is that right?
A. I cannot.
Q. Earlier this morning I had asked you about the extent to which you had developed some opinions regarding Dr. Smith's supplemental declaration and I think you said "Sure, I have." And as I've already told you, I don't have that in front of me. But if I could, I would like for you to go through with me and describe your opinions that you developed in response to Dr. Smith's supplemental declaration.
A. Okay. Do you want to get a copy? I only have one, but I'm sure someone could track one down for you.
Q. That'd be helpful if there are any volunteers in the studio audience. But if not, I'll struggle through.
A. Okay. The first one, and really this is probably the most, well, it's one of the most important, is Dr. Smith's insistence that because APL is classified as a subtype of AML, ergo, they all are going to have the same etiological risk factors and they're all basically going to be the

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same disease. And that is just clearly not the case. So I think I strongly disagree with that notion.
Q. And you expressed that opinion in your original report. Correct?
A. I did. But then he brought it up --
Q. Right. And I'm not trying to criticize. I just want to make sure.
A. Yes, I did.
Q. And I want to clarify. The materials you would rely on for purposes of your opinion that APL is a separate disease are the same materials that you mentioned in your original report. Is that correct?
A. Yes.
Q. All right.
A. So, yeah, that shows up two or three more times. Then I have some issues with his referencing, this is in paragraph 6, and his sentence reads "Common genetic variants in a gene called NQ01 confer susceptibility to AML and two studies in England and China show that this is strongest for de novo AML cases harboring translocations and inversions, including translocation 15;17 in APL."

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That is worded, perhaps not intentionally, but that is very misleading because it is implying that there is a strong link between the 15;17 and this NQ01 mutation; and when you pull those studies and look at them, that is not the case. In fact, 15;17 is the weakest of all of the different translocations that are listed there. There's no way you can look at that dataset and say this is the strongest association.

Then there are some other things that he put in that paragraph, but it's kind of a so-what; it's really just not that relevant.

Then he goes on at the bottom and says "Thus, common environmental causes are likely for these leukemias and may include low-level benzene exposure, quinone compounds in our diet, ionizing radiation and chemicals producing oxidative stress."

Again, that is inappropriate. For one thing, we have been arguing all along that APL does not share the same environmental risk factors, and this notion that chemicals producing oxidative stress somehow tells you something about their leukemogenic potential, it's wrong. It just is not borne out by the scientific literature. You'd be hard-pressed to find a chemical that we have gone to

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any lengths to understand the mechanism of toxicity that does not induce oxidative stress: ethanol, ozone, acetaminophen, transition metals, Paraquat. I mean, they're just about all -- None of those are leukemogenic. So you cannot get to leukemia from a chemical that may or may not induce oxidative stress.

So that is an opinion that I have regarding his supplemental report.

Then he goes on to talk about a childhood study, a childhood leukemia study. The sentence reads "In a recent epidemiological study of childhood AML, we separated the good-prognosis AMLs with translocations and inversions from other forms of AML, and found a strong association between parental exposure to solvents and increased risk of these specific forms, again suggesting a common cause for APL and the other AMLs harboring translocations and inversions."

I can't read his mind so I don't know what he was thinking, but that study does not mention APL. There is no mention in there of a 15;17 translocation, so I don't see how that study is supportive of what he writes in this report.

And then the last sentence of that

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paragraph reads "Finally, like APL, which has a constant incidence with age in adults" and then he references Douer 2003, and that Douer is an epidemiological study that has looked specifically at APL and finds no environmental or occupational risk factors. So that supports our position more than it does his.

And Moorman, there's another reference there, Moorman, Roman 2001, "suggesting a common etiology" is what it says. The abstract of Moorman clearly says that these different cytogenetic changes have different etiologies. I mean, it is very clear that they do not share the same etiologies, so....

Q. May I interrupt you for just a moment to ask you about that last comment. Do you have a copy of that Moorman paper with you?

A. I'm sure I do. Well, I wouldn't say "sure," but....

So the abstract reads, the last sentence -- oh, here it is -- "Our results suggest that smoking-associated risk from acute myeloid leukemia is restricted to a translocation a21 q22 q23 subgroup. This supports the hypothesis that distinct cytogenetic subgroups of acute myeloid

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leukemia have separate etiologies." Which is pretty much what I've been saying all along.

Q. Okay, go ahead.

A. Let's see. In 7, "The notion that benzene cannot cause APL is refuted by the limited available epidemiological literature," that's his reading. He talks about the most well-known study, the Travis study -- Well, actually what he says is "The most well-known epidemiological cohort studies of benzene-exposed workers outside of China do not provide information about different subtypes of AML and consider AML as one disease," and then he lists several. But Cuneo and Middleman and Fagioli and these others, they're small studies, but they have done exactly this. They have gone in and said, well, what do these occupational leukemias look like and what cytogenetic changes do we see? And they all have some relevance to this question. They're small studies, I'll allow that.

Let's see. This is reading Dr. Smith's supplemental report: "If APL were really so different from AML, why is it not listed as a separate cause of death on death certificates and why are there no epidemiological studies that focus only on APL and benzene exposure?"

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Well, I disagree. I think there are and I think he has identified some of them; and we just talked about one with Douer. Why they are not listed as a separate cause of death on the death certificates, I don't know the answer to that. I don't think you can rely too heavily on what's written on those death certificates based on what I know about how sometimes or at least historically they were produced.

Then in paragraph 8 he writes "The notion that benzene cannot cause APL is refuted by the limited available epidemiological literature because APL is seen in studies of workers exposed to benzene where the subtypes of AML have been separately analyzed." Well, he just said, the page before, that that had never been done, so I don't get that. That's sort of perplexing. And then he goes on to say "have been separately analyzed and has been found at higher levels than expected with an odds ratio that exceeds 2."

Well, he's referring to his own sort of behind-the-scenes calculations that may or may not be right, may or may not be appropriate, but they were not part of that study. And we have already talked in some detail about Mele, so there's really

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no point in getting into that. He cites it as evidence to support it, and I strongly disagree that that study supports anything.

The Golomb calculations and this whole debate over Golomb is even less -- I mean, there's only one case of APL in that study. There's one case of APL in the exposed, there's four or five cases of APL in the unexposed, and yet somehow we are expected to accept that this stands for the proposition that exposure can cause this disease. I just don't accept that. I think Dr. Garabrant has gone into some detail about the math and the appropriateness of the math, so I don't need to do that.

So now I'm on 13, paragraph 13. Let's see. I've got a bunch of things.

So what he writes is "Hydroquinone and its oxidation product 1,4-benzoquinone have been shown to cause chromosome damage and toxicity to a greater extent in stem cells than in lymphocytes." That again is somewhat misleading. He did publish a paper where his definition of a stem cell was a CD34 positive marker and he saw some differences in potency between CD34 positive cells and CD34 minus cells.

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That is really the only evidence that I can think of, and even there it wasn't consistent. Lots of his markers, that wasn't true. There were CD34 negative cells that were more susceptible. And in real workers and exposed workers, lymphocytopenia has consistently been shown to be the most sensitive endpoint. So this notion that lymphocytes are far less susceptible than bone marrow stem cells I don't believe is supportable by the scientific evidence.

He referenced a couple of papers there, Abernathy from 2004, which really doesn't address this issue, and compares stem cells with lymphocytes but does in fact talk about different cells of origin, which is kind of what we've been discussing earlier today.

I think Dr. Garabrant has gone into some detail regarding the Travis study and whether or not Dr. Smith's sort of behind-the-scenes interpretation and mathematical calculations of that cohort are appropriate. I happen to think they are not. I think there are a lot of things wrong with that cohort, but we don't need to go into it if it's already been discussed.

So in paragraph 16, and this is getting to really what we discussed earlier, he writes about

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Dr. Garabrant: "Overall, his critique could have some validity if APL were a separate disease, which it is not; it is a subtype of AML." And that's just too simplistic of a view.

If you look at other collective groupings of diseases such as non-Hodgkin's lymphoma, whether it's 25 or 26 different forms that go into that category, they absolutely have different etiological risk factors. And the more people start separating out that division, the clearer those distinctions become evident. The same with myelodysplasia. It is a very heterogeneic group of diseases and it is becoming more and more evident that they have clear distinctions in their etiology. Epidemiologists will catch up and they will stop these collective groupings of diseases for this very reason. It's happening now with these others and it will happen with AML as well. So, a little soapbox there, I guess.

Q. The form of my question has invited that.

A. Yeah, and then there's some other discussion about his use of proportions as opposed to the incidence rate in the Chinese population with regard to APL. When he calculates his odds ratio of 2.5, there is no statistical analysis; there's no

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confidence interval. There's no indication, really, of what that means. And I don't think that that supports his bolded conclusion that one can say to a reasonable degree of probability that the odds ratio for APL associated with benzene exposure in the Chinese cohort is more likely than not greater than 2. I just disagree with that.

This whole notion of the healthy worker effect with regard to the Chinese cohort doesn't make any sense, as if you look at the overall mortality in that cohort, the workers have a lower mortality or a higher mortality than the controls. So, if anything, it's going the opposite direction. It would be an unhealthy worker effect as opposed to a healthy worker effect. That doesn't make any sense.

And then in 21, paragraph 21, he writes "Both Dr. Bennett and Dr. Garabrant criticize the pathology review in the Travis et al. study, but they ignore the difficulties of performing such research in China in the time period before 1987."

Well, I don't know whether they ignore the difficulties of performing that research or not, but whether they did or they didn't, it's irrelevant. The pathology is inappropriate for the conclusions

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that Dr. Smith is drawing from it, and that's really their point.

And then I think he starts talking about me. Yes.

I think he is misinformed on the smoking, the cigarette smoking literature. I think that smoking literature is pretty clear in that the different subtypes of AML have different risk factors and that smoking is associated with AML, according to just about every organization out there. But if you look at those studies where they have separated out the subtypes, APL is not one of them. In fact, APL in at least two studies is statistically significantly decreased in smoking populations.

So whether you want to argue about the benzene in the smoking and whether that has anything to do with it, it's clear that there are differences between APL and the other subtypes of AML with regard to this particular risk factor. So this whole paragraph, I think he's wrong. He just has not looked at those studies carefully enough. There are at least three that support that position and there are none that are on the other side of that argument which would say yes, APL is in fact

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elevated right along with the other subtypes.

Now a semantical argument about whether I said what he said I said, and it's not really --

MR. LEGHORN: What paragraph are you referring to?

A. Oh. 25. He said I said this, and I really didn't say that, but it's not really worth going into.

Okay, in paragraph 26 he questions the relevance of me bringing up the alkylating chemotherapeutic literature and dismisses it as being irrelevant. And I disagree with that. There are many investigators, and he has even written some things in the past that would suggest that he also at one point at least felt the same way, that benzene-induced leukemias seem to follow that path and that what we have learned from alkylating chemotherapy does have relevance and bearing on what we would expect a benzene-induced leukemia to look like. And in that case you see virtually no APLs.

Okay, paragraph 27 is somewhat the same. He is quite dismissive of my arguments over threshold, which I still stand behind firmly. His citation or the references that support his position that there is no threshold are the USEPA and the

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California EPA, which is somewhat of -- it's an interesting choice, since both of those organizations as a matter of policy use the precautionary principle, so they're making decisions based on science policy, not based on scientific data.

You get outside of the regulatory agencies and I'm not aware of very many, if any, toxicologists in the field who would argue that a threshold is a hypothetical entity. In other words, there is in fact a threshold. And even if you get to the EPA and you see how they regulate chemicals, they don't explicitly say, yes, we think there's a threshold, but they regulate it as if there is.

Okay, so those organizations make decisions based on policy. That was my point.

Okay, I'm not conceding the point that I raised with regard to bimolane potentially confounding the NCI study. I think what Dr. Smith said is correct, that you would expect to see the same effects on both the control and the exposed population. But if you don't account for a known confounder for this disease in that population, you don't know whether it affected the results or not. That's my point.

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He cannot say definitively that it is the same, and so it is -- If you went to China now, knowing what we know, and you are going to do an epidemiological study on anything that had to do with APL, it would be ridiculous to ignore bimolane and to not ask the people, have you used this drug in the past? It wouldn't get published. So I am not willing to concede that point, although I think he raised an interesting argument and I think he's right on that one.

Okay, with the 15;17, it's kind of some discussion in paragraph 29 and it's this and it's that and we did this, but the bottom line is: Does it change? And that is, there is no evidence that benzene causes 15;17. And that was my point.

This is kind of semantical too, but I say -- which he apparently took issue with in paragraph 30 -- that in the report that he and David Eastmond and colleagues wrote in 2002 that the 15;17 translocation was not even discussed. And then he wrote "I would refer him to Table 2 in that publication, which lists the abnormal karyotypes" blah blah blah. Okay. It doesn't change the fact that he didn't discuss it, which he did not.

So this is a review paper in 2002 of all

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of the cytogenetic changes that people think are caused by benzene, and it was not even a topic of discussion in that paper. The studies that he lists in Table 2 do break out the subtypes, but these are the ones that we have talked about, Cuneo and Middleman and Richardson and some of these others, and, yes, there's one in the unexposed, but then there's four or five -- I'm sorry -- there's one in the exposed but there's four or five in the unexposed. That supports my position, not his.

Okay, and question -- excuse me -- paragraph 31 is talking about China and he says "However, my point is that benzene, like topoisomerase-inhibiting drugs, can induce APL." He's wrong. It doesn't. And then -- Oh, and then his argument "Such an event may have a biological threshold but will not have a population threshold and is likely to occur only in highly susceptible individuals." I don't even know what that means. And I'm not trying to be cute. I really don't know what he means by that.

Okay, and paragraph 32, he writes "This more likely than not explains why 11q23 translocations are not usually observed with benzene exposure." I agree with that, that you don't see

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it. However, "I conclude" -- and I'm reading from his report -- "I conclude that arguing that benzene doesn't produce translocations at 11q23 and therefore is not a topoisomerase inhibitor in humans is invalid and it lacks any foundation."

That's not what I said. What I said in my report was that it was inconsistent with what we would expect a topoisomerase inhibitor to be doing, that the 11q23 in 80, 90 percent of the AMLs associated with etoposide exposure display that cytogenetic change and you don't see it in benzene workers. And if you look at the structure of etoposide and you actually follow through the metabolism of etoposide, it produces catechols, it produces quinones, it produces semiquinones and hydroquinones. It produces all the same structures that you would associate with benzene metabolism. So you would look at that and think, if it's going to be doing this, it's going to be doing it as etoposide. It's going to act as that mechanism based on the structural similarities, and so far that has not been borne out by the literature.

Q. Let me stop you just a second, Doctor, with respect to that issue. How many studies are you aware of that have looked for 11q23 in benzene-

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exposed workers?

A. Just the one that I'm aware of.

Q. Go ahead.

A. And this is where I'm out of date and Jandl's textbook is out of date and we need to pay more attention to the leukemic stem cell theory. And that certainly has been an important development in experimental hematology, but it doesn't change the fact that there are different cells of origin for these diseases. So, really, you kind of got to this one earlier in our discussion, so there's not much point in going through this.

He did say something kind of confusing to me in the report, his supplemental report. This is in paragraph 33: "All active researchers that I know in this field understand this concept and do not debate whether benzene causes only some forms of AML and not others." And then at his deposition what he really meant by that was that they're just not out there talking about it, not that they totally accept his view. It's just they're not talking about it.

Well, I disagree with that. I have been in many conversations with people where this is a topic of conversation and people are very interested

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in these different subtypes and there are going to be studies that will be coming out in the next year or two where they are going to be doing subtype analysis. So this is not a moot point and just some esoteric question that we're bringing up for the purposes of this litigation; it is a legitimate hematopoietic question.

Then the last one was "In conclusion, I find Dr. Pyatt to be in error on many points, and I find most of his criticisms of my original report to be invalid." So maybe, you know, which ones did he find to be valid? I couldn't tell. He said he finds "most" of them, so there must have been some that he thought were legitimate and I don't know what those are. Okay.

Are you sorry you asked?

Q. No, I'm not. Thank you, Doctor.

A. Do you want this?

Q. Actually, you can go ahead and keep that.

MR. JENSEN: What I would like to do is take a five-minute break; and after that break I anticipate I will have a few minutes' more worth of questioning, but I don't think we're going to need to take a lunch break.

MR. LEGHORN: Okay.

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(In recess 11:29 a.m. to 11:39 a.m.)

BY MR. JENSEN:

Q. Dr. Pyatt, have you reviewed Carl Cranor's two reports in this case?

A. I read them.

Q. I am going to read to you a portion from Dr. Cranor's supplemental declaration, on page 3, at paragraph 6.

A. Go ahead. I'm going to track it down.

Q. All right. The second sentence of paragraph 6 says, "As my earlier report indicated, 'An expert reviews the body of data that appear to bear on causal judgments, selects the scientifically relevant data, assesses and weighs studies for their quality, weighs the importance of different kinds of data vis-à-vis one another, e.g., animal studies versus human studies versus short-term studies versus structure/activity relationships versus mechanistic evidence versus any case studies and so on, and brings her background understanding of biology and toxicology as well as her understanding of the phenomena to the causal issues." Do you agree with that statement in Dr. Cranor's report?

MR. LEGHORN: Object to the form.

A. I like the "her understanding." Sure,

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yes.

Q. Next sentence says "Scientific judgment also enters into integrating all the data and how it bears on evaluating different possible explanations in light of all the evidence and the particular phenomena to be explained, e.g., a disease." Do you agree with that statement?

MR. LEGHORN: Object to the form.

A. I agree with that.

Q. Paragraph 7 is the next paragraph and it says "One practical import of this inferential process is that there are numerous places for scientific experts to disagree." Do you agree with that?

MR. LEGHORN: Object to the form.

A. Well, I mean, it's a little vague. It depends on what the issue is that you're talking about whether or not you're going to find numerous places for scientific experts to disagree. So it's hard to know yes or no on that one.

Q. Okay. Then in the following sentences he gives some examples and we'll see if you agree with any or all of his examples. He says "They can select somewhat different studies for consideration." Do you agree with that?

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MR. LEGHORN: Object to the form.

A. He wrote "They can assess the same studies" -- Oh, no, there it is, "They can select somewhat different studies for consideration." I don't understand that. Why would they do that? Why would people select different studies? We all should be looking at all of the data that's out there. You wouldn't be picking data that supports your opinion and ignoring the rest.

Q. Okay. He says, the next sentence, "They can assess the same studies somewhat differently or give studies of the same kind, e.g., epidemiological studies, somewhat different emphases or weight." Do you agree with that?

MR. LEGHORN: Object to the form.

A. Well, "They can assess the same studies somewhat differently," I think that's absolutely true based on your background and your training and what you're looking at, "or give studies of the same kind somewhat different emphases or weight." Well, again, that's so vague, it's hard to really know what he's talking about, but I think that's probably right.

Q. And he attempts to clarify, I think, with his next sentence: "That is, one scientist might

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give one study or set of studies greater weight than another scientist." Do you agree with that?
MR. LEGHORN: Object to the form.
A. Well, I mean, I think that there is a general consensus in the scientific community about the relative weight of data and while you might have one person who says I believe this mechanistic study is the most important piece of data out there, that isn't generally considered the hierarchy of power, if you will, of these scientific studies. So I think there is general consensus on how you should rank scientific and epidemiological data, particularly with regard to understanding the potential between chemical exposure and a disease that may not arise for five or ten years.
Q. The next sentence says "When they need to draw overall conclusions and integrate different kinds of evidence, they can weigh and evaluate different kinds of studies, e.g., epidemiological studies v. animal data v. mechanistic data, differently." Do you agree with that sentence?
MR. LEGHORN: Object to the form.
A. I think that's kind of the same thing that we just said earlier. I mean, I think there is consensus depending on the relative weight of, say,

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these three piles of data here depending on what you're trying to do. And if what you are trying to do is understand whether or not benzene is causally linked to an increased incidence of APL, the epidemiological data is the most important. The EPA and other regulatory agencies, if they are trying to calculate a cancer slope factor for a particular chemical, they will frequently use animal data because you have better quantitation. You have better doses and better control groups and they can get a clearer dose response, whereas with the epidemiological studies they frequently can't do that.
If you wanted to understand how does my drug work, then the mechanistic data is probably going to be the most important for that particular question. So depending on what you're going after, then you would probably rank these things differently. I think for the question on the table right now, I don't think there would be much disagreement about how you should be evaluating, for example, these three cases, these examples in answering this question.
Q. Do you have any citations to literature to support your statement regarding the hierarchy of

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different kinds of data with respect to general causation questions?
A. The hierarchy of -- ? I think it's pretty standard epidemiological methodology and you would find something to that effect in any epidemiology text. And I think it is consistent with the Bradford-Hill criteria or statements or comments or whatever you want to call that list of the way to evaluate scientific data. I think it's all consistent.
Q. The last sentence of paragraph 7 says "As Kuhn indicated for theory choice, there are no algorithms, there has been no progress on algorithms, and quite good well-qualified scientists can and do disagree." Assuming that Dr. Cranor intended that sentence to apply to scientific inquiry into general causation questions with respect to chemical exposures and disease, do you agree with that statement?
MR. LEGHORN: Object to the form.
A. I don't know what that statement means. I don't know who Kuhn is. I don't know what this theory choice is. I don't know what he's referring to. I can't take that sentence and superimpose it over your question. They just seem very different

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to me. So, I mean, I'll try to answer your question, but I don't know what this sentence means.
Q. Okay.
Dr. Pyatt, has any of your research with respect to benzene and its metabolites been funded in whole or in part by industry?
MR. LEGHORN: Object to form.
A. Well, I don't know the answer to that question. When I was working on those studies with Rich Irons, we had two government grants from NIH and there was also some API money. And where the money came from to fund those specific experiments, I don't know. It could have been either one. My gut feeling is that it was from NIH, but it could have been from API.
Q. Was Dr. Irons your graduate adviser?
A. Yes.
Q. How many articles have you published relating to benzene and its metabolites since you left Dr. Irons' research group?
A. None.
Q. When was that that you left Dr. Irons' research group?
A. Well, it was kind of a transition. You know, I started getting grants on my own and paying

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my own salary and started working on other things probably 2000, 2001. I don't honestly remember when I stopped receiving any support from Dr. Irons' grants, but it was somewhere around that time frame.
Q. How would you describe the focus of your own research today?
A. My research today or how would I describe it throughout time?
Q. Well, let's put it this way. How would you describe the focus of your research since you left Dr. Irons' research group?
A. I have always been interested in bone marrow toxicity and hematopoiesis and so my research funding for the two or three years after when I was at the university were dealing with hematopoiesis and hematopoietic stem cells as therapeutic targets and toxicity associated with those therapeutic targets. I have also been -- I'm sorry. Toxicity associated with some of the storage methodologies for those therapeutic targets. Immunotoxicity, I had a grant to look at that.
Since I left the university full time in 2003 or 2004, then I have been mostly in a consulting role and had limited affiliation with bench, kind of wet biology. And then the kind of

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research that I have done recently has been dealing with published data and not necessarily generating my own data per se.
Q. So you would characterize your current research as evaluation of other people's published data, published research. Correct?
A. I think, yeah, that's reasonable. And we have some studies and things going on where we get to look at new data, but it's harder.
Q. Is it fair to say that in your role today as a consultant, that a fair number of the projects that you've become involved with in evaluating published data include data published by Dr. Martyn Smith?
A. No.
Q. Would you agree that there is no algorithm available instructing scientists investigating issues of general causation how to apply the Bradford-Hill factors to a given set of data?
MR. LEGHORN: Object to the form.
A. Could you define what you mean by an algorithm? Do you mean like a precise road map on how to use those -- ? Go ahead. Define algorithm.
Q. Yes, let's say that that's the definition of algorithm.

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A. Okay. I'm sorry. What's your question again?
Q. Whether you believe there is no algorithm as you've defined it for purposes of instructing scientists who are evaluating general causation questions as to how to apply the Bradford-Hill factors.
MR. LEGHORN: Object to the form.
A. No, I wouldn't agree with that.
Q. And what is the algorithm?
A. Well, I mean, I think when you read through these criteria, you read his paper, it's pretty clear what you should be doing. And he's not the only one. There's Paustenbach and there are others that go through the same evaluative process, here's how we look at that data, and I don't think that there is that much disagreement about how you should go about doing that.
Q. Would you agree that there is no algorithm available to assess the relative weight of one epidemiological study versus another?
MR. LEGHORN: Object to the form.
A. There's that word again. I mean, I think epidemiologists and scientists that are looking at human data, there are criteria by which you can rank

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and think about the strengths of these various studies based on the size and their appropriately taking care of confounders and all of the other aspects. I mean, I think there is still a criteria that can be used to evaluate the relative ranking.
Q. Does any such relative ranking in your view still depend upon application of the subjective scientific judgment of the researcher who's doing the evaluation?
MR. LEGHORN: Object to the form.
A. Say that again?
Q. I'm not sure I can get it out again. I'll try.
Would you agree that any scientist who is assigning relative weight to be given to one epidemiological study versus another must in the course of that evaluation exercise subjective scientific judgment as part of that exercise?
MR. LEGHORN: Object to the form.
A. No, not the way you worded it. I mean, again, I think that if you're just looking at epidemiological data, it's going to depend on the question that you are trying to address. But I think it is generally accepted across the board that cohort studies are going to be the best data, case-

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control studies secondary to that, and case reports at the bottom of that pile. And I don't think there's going to be much subjectiveness in terms of that ranking depending on what question you're asking. If it's a rare disease, then other things than case-control studies might be the only way to go about it. But I still think that ranking holds.
Q. With respect to APL specifically, would that qualify as a rare disease under whatever definition you were using in your last answer?
A. Well, I didn't have a precise line drawn in the sand to say it's rare or not rare. We already talked about this: I think APL is a rare disease.
Q. Within the category of cohort studies and comparing one cohort study to another and trying to assign the relative weight to give to one cohort study versus another cohort study, would you agree that that process necessarily requires the exercise of subjective scientific judgment?
MR. LEGHORN: Object to the form.
A. My answer to that would really be twofold. First is, that type of comparison is within the purview of an epidemiologist, and I don't get into that very often. But I do not believe that that

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comparison would be subjective. I think it would be based on a set of objective criteria that everyone would identify and know what they're talking about and not I like this one versus I don't like that one because it supports my opinion or whatever the subjective reason is. It's going to be based on the size and the statistical power and all these other things that the epidemiologists would evaluate.
Q. But you would agree that, despite the existence of objectively definable criteria by which to assess the issue of which study is worth assigning more weight to than another, that reasonable scientists can and do disagree about that issue all the time?
MR. LEGHORN: Object to the form.
A. No, I don't agree with that.
Q. You don't? You don't agree that reasonable scientists assign different weight to one cohort study versus another with respect to issues of exposure and disease?
A. Based on --
MR. LEGHORN: Objection, argumentative.
A. Based on objective criteria, perhaps. But it shouldn't be occurring on this subjective criteria that you were talking about, whatever that

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is.
Q. Well, here's the point. Even if both experts agree that there are a set of objective criteria to apply in assigning weight to studies, the two experts might apply those criteria differently. Right?
MR. LEGHORN: Object to the form.
A. There might be subtle differences. But I wouldn't think there are going to be differences on the big issues. You know, is this a big enough study to address this question? What is the statistical power? Those kinds of things, you know. Are the confounders identified? Have they been stratified out? Those kinds of issues, no, I don't think there is going to be much discussion on that. Whether you're happy with the conclusions or are the conclusions supportable by the data, yeah, you might have some disagreement there.
MR. JENSEN: That's all I've got for you today, Dr. Pyatt, unless somebody else wants to ask questions.
MR. LEGHORN: I don't think so. Any questions? Any questions on the phone?
The hammer comes down. Done.
(Deposition concluded at 12:02 p.m.)

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COURT REPORTER'S CERTIFICATE

I, J. Edward Varallo, RMR, CRR, Registered Professional Reporter and Notary Public in the Commonwealth of Massachusetts (my commission expires 12/24/2015), hereby certify that the deposition of David W. Pyatt, Ph.D. taken on February 19, 2009, in the matter of Brian K. Milward and Linda J. Milward v. Acuity Specialty Products Group, Inc., et al. was recorded by me stenographically and transcribed; that before being sworn by me, the deponent provided satisfactory evidence of identification as required by Executive Order 455 (03-13) of the Governor.

I certify that the deposition transcript produced by me is true and accurate to the best of my ability.

I certify further that I am not counsel, attorney, or relative of any party litigant, and have no interest, financial or otherwise, in the outcome of this suit.

DATED: 2/25/2009 J. Edward Varallo

WITNESS: David W. Pyatt, Ph.D.
DATE: February 19, 2009
CASE: Brian K. Milward and Linda J. Milward v. Acuity Specialty Products Group, Inc., et al.

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