UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

)
BRIAN K. MILWARD, et al,)

)
Plaintiffs,)
) Civil Action
v.) No. 07-11944-GAO
)

ACUITY SPECIALTY PRODUCTS)
GROUP, INC., et al,)
)
Defendants.)
)

BEFORE THE HONORABLE GEORGE A. O'TOOLE, JR.
UNITED STATES DISTRICT JUDGE

DAUBERT HEARING - DAY 2

John J. Moakley United States Courthouse
Courtroom No. 9
One Courthouse Way
Boston, Massachusetts 02210

Wednesday, April 22, 2009

9:30 a.m.
Marcia G. Patrisso, RMR, CRR
Official Court Reporter

John J. Moakley U.S. Courthouse
One Courthouse Way, Room 3510
Boston, Massachusetts 02210

(617) 737-8728
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I N D E X

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P R O C E E D I N G S

THE CLERK: All rise.

This is the continuation of the Daubert hearing in Milward.

Counsel, please be seated.

THE COURT: Mr. Stewart?

MR. STEWART: We're ready?

THE COURT: We're ready.

MR. STEWART: At this time we would call to the stand Dr. Carl Cranor.

CARL FOREST CRANOR, sworn

THE CLERK: Please be seated. State your name.

THE WITNESS: My name is Carl, with a C, Forest Cranor.

MR. STEWART: Your Honor, I know that this morning we will probably be using this ELMO exclusively, so I don't know how to get it going.

THE COURT: All right.

(Pause.)

THE COURT: I think there may be a toggle of some kind that you need to set on the base.

Why don't you call Phil.

How soon do you need it?

MR. STEWART: We can get started. I'll need it fairly quick but -

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THE COURT: I think it's going to be a fairly quick answer as long as someone comes with the background knowledge.
MR. STEWART: Okay.
MR. LEGHORN: The expert with the know-how.
MR. STEWART: Let's get started, and when we need it we'll stop.
DIRECT EXAMINATION
BY MR. STEWART:

Q. So please tell the Court your name.
A. My name is Dr. Carl Cranor.
Q. And, Dr. Cranor, please tell the Court your occupation.
A. I'm a professor of philosophy at the University of California, Riverside, holding the title of Distinguished Professor of Philosophy.
Q. So I know the Court has told us that the Court's read your CV and knows that background, so here's what I want to do. We know you have an undergraduate degree in mathematics. We know you have a Ph.D. in philosophy from UCLA. We know you have a master's of study in law from Yale. And what I would like you to do is to inform the Court on what the focus of your time and attention has been over the last 27 years pertaining to the application of logic and reasoning within philosophy and its relationship to science and causation analysis.
A. For the past 27 years I've been interested in scientific inferences and how scientists come to conclusions about
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causation, focusing particularly not on abstract questions the way philosophers of science might but on particular causal judgments that are rendered for purposes of public health or tort litigation and so on.
Philosophers are trained in various kinds of -- two major kinds of reasoning. One is deductive logic, which I indicated in my report. A simple example would be A equals B, B equals C, therefore, A equals C. That's a deductively strong argument.
There's another group of arguments called non-deductive arguments, which I call, for purposes of recent work, inference to the best explanation; some people call them diagnostic induction. But what I found is that scientists -- which is the case -- scientists -- as exemplified as the International Agency for Research on Cancer, or the next, National Toxicology Program, which we'll refer to mostly as NTP -- utilize inferences to the best explanation in trying to understand or explain causal relationships that affect -- particularly affect public health.

Q. Okay. Now, you studied in this area, published in this area, I know. And what I want to know is from your studies and publications and teachings, has that led to you being elected as a fellow of the American Association for the Advancement of Science in 1998?
A. Yes, it has.
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Q. And also, you were elected as a fellow of the Collegium Ramazzini; is that true?
A. That is correct.
Q. Why don't you briefly tell the Court what that is and why it is important or instructive as it relates to science methodology, the concept of causation?
A. The Collegium Ramazzini is an international group of what -- this is what their charter says -- an international group of scientists who seek to bring science to the -- to protect the public health. It is a very small group of scientists; 180 members would be the max. And rumor has it -informed rumor has it that it's based on the number of cardinals that the Pope has in the Vatican. So since its home is in Italy, there's a close analogy there to the cardinals and the Pope.
The current -- I don't want to use the word "Pope" -president of the Collegium Ramazzini is Philip Landrigan.

Q. In connection with the Collegium Ramazzini, this group takes a look at scientific issues and causation related to cancer and other things, true?
A. Cancer typically -- cancer is a very common one, but other diseases as well, seeking to bring the best scientific evidence to bear on public health issues.
Q. Okay. Now, you've also served on scientific advisory panels, correct?
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A. That's correct.
Q. And in your role on those panels, was your role in part to help focus the panels on the proper scientific methodology from a broad sense of logic and reasoning to be employed for causation analysis?
A. Yes. I think that's a reasonable characterization. Since I've spent a considerable amount of time studying and trying to understand how -- the kinds of evidence, the patterns of evidence, the reasoning and forms of reasoning that scientists use to infer a causation, I've become acquainted with a wide range of patterns of evidence. And that seems to be valued on science advisory panels. It's just -- it's not on my vitae, I don't think, and it was not in my report, but I've just been appointed also to the Nanotechnology Panel for the State of California.
Now, the way this might manifest itself in a very clear way, several years ago I was on the Electromagnetic Fields Panel for California. And the question there was whether -- to what extent one could make an inference whether electromagnetic fields posed health risks. And we -- there were actually quite heated discussions on the science advisory panel because you had three groups of scientists: You had the epidemiologists, you had the animal study people, and you had the physicists who were interested in the biophysical mechanism by which magnetic and electrical fields could affect human tissues or mammalian

tissues.

And what was interesting about that, some of them didn't have a very wide perspective on what would bear on causation; for example, the epidemiologists would say, "Well, we have these different epidemiological studies done by different people in different circumstances and they keep pointing to a low level, a low relative risk, from exposure to certain kinds of electromagnetic fields." On the other hand, you have the biophysicists there saying, "It's absolutely impossible, can't be done."

And so there was a role there to stay, "Look, when we consider the broad range of evidence" -- human evidence won't go away, biophysical evidence, which doesn't seem to be there, and animal evidence -- "why should we even conclude?" So having a broader perspective, actually, permitted me to make a contribution to that discussion, contrary to some of the -what I saw as kind of tunnel vision on the part of some of the subgroups there.

Q.
Okay. Now -THE
COURT: Mr. Stewart, we have our expert here.
MR. STEWART: Great.
THE COURT: Maybe you can...
(There is an interruption in the proceedings.)
BY MR. STEWART:

Q. All right. I noted in your CV that over the past 27 years
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you've published 50 articles, book chapters on issues -philosophic issues relating to the interface of risk, science and the law. And in those publications do you deal with the issue of how scientists should be thinking about causation analysis and application of the principles of logic and reason?

A. Yes. I began with the idea of making an inference to the best explanation. And this general -- this general inference form that philosophers have been trained in, both places constraints on the kind of evidence you would seek. The evidence you need for understanding why an airliner crashed is rather different from the evidence you need for the health effects from exposure to arsenic or something like that. It invites certain kinds of evidence, rules out other kinds of evidence, unless there's a special form of argument.
So I've looked at the kinds of arguments that scientists have offered in terms of distinguished scientific committees at the International Agency for Research on Cancer and at the National Toxicology Program and use them as kind of models. And that corresponds with what you might expect from considering inference to the best explanation. There are certain kinds of evidence that would generically be considered for making assessments of health effects. You would look at any human evidence that have; you would look at the animal evidence that you would have; you would look at mechanistic evidence, genetic evidence. There's different ways of dividing

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it up. And there's a wide range of evidence that can help one come to conclusions about causation.

Q. All right. Now, you had talked about IARC and NTP, and we'll talk about those in greater detail a little later. But in the course of your studies, your publications and your teaching, I take it that it's fair to say that you have studied extensively how those bodies went about making determinations on causation and cancer and the kinds of evidence they looked at?
A. That's correct.
Q. Okay. Now, I also noted on your CV that you participated in an international workshop specifically reviewing Bradford Hill's paper, "Environment and Disease: Association or Causation"; is that correct?
A. That is correct.
Q. And you actually gave a lecture -A.
I gave a presentation to them. The idea -- this was sponsored by the European community, but they wanted to revisit Bradford Hill 25 years on and see what had been learned, what had changed, and issues and correctives for some of the ways that Bradford Hill had been used out there.
Q. And at that workshop, representatives from IARC were there?
A. That's correct.
Q. As well as representatives from the U.S. National
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Institute of Environmental Health Sciences, correct?

A. I believe that's correct.
Q. Okay.
A. I believe members of the European community, more broadly.
Q. Now, you've written other books. I've brought one of them, "Toxic Torts: Science, Law and the Possibility of Justice." And within this book is there a chapter dedicated to this very topic of causation, scientific causation, and how it's reached by your use of inference -A.
Yes, there is a chapter -- I forgot the name, but something like "Scientific Evidence for" -- "Studies of Toxicity and Scientific Reasoning," I believe is the title.
Q. Okay.
A. Yes.
Q. So here's what I want to do: With that background in mind, I want to turn to the issue of how science considers whether a chemical or substance causes a disease or cancer. And we'll focus on cancer since I want you to focus on IARC and the National Toxicology Program issues.
And so the first thing I would like you to do is I would like you to explain to the Court the National Toxicology Program in the United States through the Department of Health and Human Services and their Report on Carcinogens, just generally -

A. The National Toxicology Program, by its website, indicates

it's an interagency group of scientists that's charged roughly with finding substances, but including carcinogens, that may present issues of public health. And it issues -- I think it was supposed to issue maybe every two years -- a Report on Carcinogens. As with many such reports, they fall behind, but I believe the 11th Annual Report on Carcinogens, which lists all the carcinogens and the evidence they have for it in a book, is the latest. Volume 11 is the latest.

Q. And I've got that with me, 11th Report on Carcinogens, 2004. What I would like to do, Dr. Cranor, for the sake of time, is I would like to show you and the Court portions of this document and then have you either further explain or tell from your background, study what this means and how it relates to scientific causation. Can we do that?
A. Yes. Yes.
Q.
Okay. So -MR.
STEWART: Is that supposed to show up here?
THE COURT: It will now.
BY MR. STEWART:

Q. Can you see that all right?
A. I can see it fine.
Q. What I would like to do first is read this portion that says "Listing Criteria." It says, "The criteria for listing an agent, substance, mixture or exposure circumstance in the RoC" -- that's Report of Carcinogens?
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A. Correct.
Q. -- "are as follows." And it says, "Known to be Human Carcinogen." "There is sufficient evidence of carcinogenicity from studies in humans" -- and there's an asterisk there which we'll get to in a moment -- "which indicates a causal relationship between exposure to the agent, substance or mixture, and human cancer."
Now, what I would like to do is try and -MR. LEGHORN: Can we have the page you're on?
MR. STEWART: Yes. It's I-2.
MR. LEGHORN: Thank you very much.

BY MR. STEWART:

Q. -- is go down to the asterisk and read that and then ask you a question about it. The asterisk which was next to "Studies in Humans" says, "This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people."
Now, is that the standard that the National Toxicology Program Report on Carcinogens uses in determining whether something is a known human carcinogen?

A. Yes.
Q. And based on that reading, and also your research that you
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have done in connection with this issue, is it -- does the National Toxicology Program require statistically significant epidemiologic studies of a substance and a particular cancer -or cancer in general -- to make the determination that that substance is a known human carcinogen?

A. No, not according to this statement. That would be one kind of human evidence but not the only kind. They mention data from clinical studies -- I'm not quite clear what that means -- and data derived from tissue and cell cultures that bears on causation.
Q. Okay. Now, what I would like to do is go to the next category since this book not only lists things that are -- that the National Toxicology Program through the Department of Health and Human Services determines are known human carcinogens but also things that it says are reasonably anticipated to be human carcinogens, true?
A. Correct.
Q. All right. So let's read their definition of that, and then let me ask you a question about it. This says, under "Listing Criteria," "Reasonably Anticipated to be Human Carcinogen." And this is the definition: "There is limited evidence of carcinogenicity from studies in humans" -- and it's the same asterisk as we had before, true?
A. Yes.
Q. -- "which indicates that causal interpretation is

credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded."

A. Correct.
Q. What's that mean?
A. Well, it means that when you have limited -- you have evidence of carcinogenicity from studies in humans -- I think there are several things that are interesting about this -- but there are various possible explanations for that. It might be spurious, because of chance; there might have been a construction of the study that let some kind of bias slip in; or they might not have ruled out the possibility that you had something else that explained what was going on instead of the thing in question that you're looking at. You couldn't rule out these other possible explanations.
Q. All right. So under the category of "Reasonably Anticipated to be a Human Carcinogen" -- again, do the National Toxicology Program and the Report of Carcinogens of the United States government require that there is statistically significant positive associations in the epidemiologic studies before a substance is determined to be a carcinogen in humans?
A. No, they're not.
Q. All right. Now, based on your studies, background, what you've written and in connection with what you've done with IARC as well, does "reasonably anticipated to be a human
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carcinogen" -- does that equate with "probably a human carcinogen"?

A. Yes, I believe that's a common understanding. I think that NTP didn't want to use quite the same language that the International Agency for Research on Cancer did, so they used "reasonably anticipated" to mean that it was probable. More likely than not, I think, is -- would be another common term.
Q. You understand those to be equivalent?
A. Roughly, yes.
Q. Roughly.
So I want to keep reading about "reasonably anticipated to be a human carcinogen" because what we've just read is not the only -

A. Correct.
Q. -- way that that can be -- a substance can fall into that category, true?
A. Correct. If I could add to that, what this shows is the variety of patterns of evidence that the National Toxicology Program will utilize for placing something in the category of "reasonably anticipated to be a human carcinogen."
Q. Okay. It says then, "Or" -- and this is another pattern of evidence, I suppose, that we'll talk about -- "there is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and
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benign tumors; one, in multiple species or at multiple tissue sites; or, two, by multiple routes of exposure; or, three, to an unusual degree with regard to incidence, site or type of tumor or age at onset."
And you don't have to go into detail about what that means, necessarily. I just have this question: In any of those descriptions there of those kinds of evidence, is it required that there is epidemiologic evidence?

A. No. This is a pattern of evidence that they utilize that's based on animal studies, no human epi studies or no human evidence necessarily of any kind.
Q. All right. There is another category that can also apply, correct?
A. Correct.
Q. So still under "reasonably anticipated to be a human carcinogen" it says, "or there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans."
A. That's correct.
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Q. And that is basically saying, isn't it, that even if you don't have human epidemiology studies, or human studies of any kind about carcinogenicity on a particular subject, or animal studies on that particular subject, it could still be listed as either a known carcinogen or a reasonably anticipated carcinogen simply by the mechanism it uses to cause cancer?
A. Yes. The way I read this is that you can have less than sufficient evidence of carcinogenicity in humans. That means that you wouldn't have really good human evidence, but it might be inadequate; it might be less than sufficient. You could also have -- and when you have sufficient evidence of carcinogenicity in humans, that means these agencies conclude that that established as a causal relationship. So what they're saying here for both humans and animals: You can't establish a human -- a causal relationship between exposure to the substance in question in either animals or humans, but you can supplement it by other kinds of evidence, and it can rise to the level of it being a probable human carcinogenic.
Q. Okay. And what I would like to do is read another section here. And we'll talk about this in greater detail, but I just want to point out that it's in the NTP. It says, after the portion I just read, "Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to," and then
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it gives a broad list of things, which I'm not going to read them for the sake of time.
But you agree with that statement?

A. I agree with that statement. The National Toxicology Program is one from whom I learned; IARC makes similar claims about the role of scientific judgment.
Q. Okay. And we'll get to that in greater detail, I think, a little later.
The next thing I would like to do, Dr. Cranor, is just show some examples of that in this, if you will. So this book's got a lot of substances in it, true?

A. That's correct.
Q. So I've picked three, frankly fairly randomly, but what I would like to do is read you this portion of -- this is acrylamide that I'm looking at -MR.
STEWART: And, Mr. Leghorn, this is 3 on page 3-4, or Section No. 3-4. It says, "Acrylamide: Reasonably anticipated to be a human carcinogen. First listed in the Sixth Annual Report on Carcinogens in 1991."
BY MR. STEWART:

Q. -- and now I want to read this section and ask you a question about it. It says, "Acrylamide is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals," and then it lists IARC '86, '87 and '94.
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Those are the references to the International Agency on Research on Cancer reports, correct?

A. That's correct.
Q. Okay. And then it gives some incidences. It says, "When administered in the drinking water, acrylamide increased the incidences of adrenal pheochromocytomas and mesotheliomas of the tunica of the testes in male rats; pituitary adenomas, mammary adenomas and adenocarcinomas; oral cavity papillomas; uterine adenocarcinomas and clitoral gland adenomas in female rats; and the follicular adenomas of the thyroid in rats of both sexes. When administered by gavage or by intraperitoneal injection, acrylamide increased both the incidence and multiplicity of lung adenomas in mice of both sexes. When administered topically, by gavage, or by intraperitoneal injection followed by long-term topical treatment with 12-O-tetradecanoylphorbol-13-acetate, acrylamide induced skin squamous cell papillomas and squamous cell carcinomas in female mice." And basically this is just animal studies?
A. It's just animal studies that are showing the difference science produced by which acrylamide causes cancer in animals.
Q. Now, it then says, "No adequate data was available to evaluate the carcinogenicity of acrylamide in humans," and it cites IARC '86, '87 and '94, correct?
A. That's correct.
Q. So in this example of acrylamide, is this an example where
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an agency that determines whether or not a substance causes cancer has reached a conclusion that that substance probably causes cancer in humans even though there was no adequate data available to evaluate carcinogenicity of acrylamide in humans?

A. That's correct.
Q. And that means no epidemiology?
A. No epidemiology or apparently no human data of other kinds, tissue studies, that sort of thing.
Q. Okay. The next example I want to go to is Furan, which is on page 3-127. And this says, "Furan: Reasonably anticipated to be a human carcinogen. First listed in the 8th Report on Carcinogens, 1998."
It says, "Furan is reasonably anticipated to be a human carcinogen based on sufficient evidence of malignant tumor formation at multiple tissue sites in multiple species of experimental animals (IARC 1995)," correct?

A. Correct.
Q. And I'm not going to read the rest of that animal data, but then it goes on to say, "No adequate human studies of the relationship between exposure to Furan and human cancer have been reported," correct?
A. Correct.
Q. Is this another example of a governmental agency, National Toxicology Program, finding that a substance probably is a human carcinogen without there being any epidemiology to
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support that -

A. That's correct.
Q. -- finding?
Okay. Then one last example. And this is the substance -- and I'm sorry, it's on page 3-168. 4,4'-Methylenebis(N,N-dimethyl)Benzenamine, it says, "Reasonably anticipated to be a human carcinogen. First listed in the 3rd Annual Report on Carcinogens (1983)."

And it says, "This chemical is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals." It says, "When administered in the diet, the chemical induced hepatocellular adenomas and carcinomas in mice of both sexes and thyroid follicular cell adenomas and carcinomas in rats of both sexes (NCI 1979)."

That's the National Cancer Institute, correct?

A. Correct.
Q. Then it says, "No data were available to evaluate the carcinogenicity of 4,4'-Methylenebis(n,n-dimethyl)Benzenamine in humans (IARC 1982)," correct?
A. That's correct.
Q. This is a third example of a governmental agency finding that a substance probably caused cancer in humans without there being epidemiology?
A. That's correct.
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MR. LEGHORN: Your Honor, can we have a page reference on that, please?
MR. STEWART: The page was 3-168.
MR. LEGHORN: Thank you, your Honor.
BY MR. STEWART:

Q. Now, we talked about there are many substances in this?
A. That's correct.
Q. And IARC goes through a similar analysis for substances as well, known carcinogens, probable human carcinogens, correct?
A. Known human carcinogens, probable human carcinogens, possible human carcinogens, inadequate evidence for human carcinogens, and then in some cases you just can't tell.
Q. Okay. Now, what I would like you to do is give the Court an idea, from what you have looked at in NTP and in IARC, in how many different instances have those governmental agencies said that there are substances that are probable human carcinogens where the governmental agencies are relying on data that is not epidemiology data in order to make that decision?
A. Well, the International -- the National Toxicology Program, the one -- when I wrote the book, I did do a count, but I didn't go through all the substances. But they listed 185 probable -- or reasonably anticipated to be human carcinogens. And what's interesting about that, for none of them do you have sufficient evidence that the exposure causes human cancer. You might have some human evidence that the
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exposure -- that it's -- it's suggested or credible that the substance causes human cancer, but these alternative explanations cannot be ruled out with a reasonable degree of scientific certainty.
And so there are 185 of them for the National Toxicology Program. And IARC has a smaller list, and it's very likely almost identical -- everything on the IARC list is likely to be included in the NTP list, but there might be something here or there missing. IARC lists, I believe, or did when I began the book, 66 substances, I believe, if I remember correctly. I could look it up. For 66 substances, they were judged to be probable human carcinogens; for 40 of those they had either inadequate or limited evidence of carcinogenicity in humans. That meant that the epi and other human evidence was not sufficiently good to call them human carcinogens.

Q. And yet based on what these agencies did, if I understand you correctly, is based on mechanistic evidence, animal evidence, evidence by analogy as we saw here -A.
Right. Structure activity.
THE REPORTER: Whoa. You're speaking over one another.

MR. STEWART: You can't talk over me.

THE WITNESS: This must be very hard going for you.

We apologize.
(Laughter.)

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BY MR. STEWART:

Q. -- that these agencies whose job it is to determine whether or not substances cause cancer in humans felt comfortable listing these as probable human carcinogens?
A. That is correct.
Q. Okay. Now, in your research in this area evaluating how these different agencies classify substances as causing cancer, have you been able to determine whether these agencies take the Bradford Hill considerations into account?
A. They do either explicitly or implicitly in trying to review the evidence that's there.
Q. All right.
A. It may be that they don't say "Now we're using Bradford Hill," but you can see that they're considering the kinds of -the aspects or viewpoints that Bradford Hill talked about in reviewing the evidence.
Q. Okay. Now, have you seen where either IARC or NTP or others you have worked with, including the California scientific advisory panels, concluded that Bradford Hill considerations demanded that statistically significant epidemiology be a prerequisite before making a judgment that a substance probably caused cancer?
A. No. Hill himself seems to disagree with that.
Q. And when you say that, what specifically are you referencing with Hill?
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A. Well, I have a copy here.
Q. Okay.
A. Does the Court have a copy?
Q. The Court has a copy somewhere. I can put -- if you'll tell me what page you're on, I can put it -A.
I'm on two page numbers, 11 and 299.
Q. Okay. And why don't you start me on the paragraph you want?
A. The paragraph beginning "Here," the second full paragraph on the left-hand column. So it says, "Here we have nine different viewpoints from which we should study association before we cry causation." People that work with -- the people that I know that have worked with Bradford Hill criteria, Bradford Hill considerations and the Bradford Hill paper, take this very seriously; they take his words very seriously here. "What I do not believe, and this has been suggested, is that we can usually lay down some hard and fast rules of evidence that must be obeyed before we accept cause and effect. None of my viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis, and none can be required as a sine qua non. What they can do with greater or less strength is to help us make up our minds on the fundamental question: Is there any other way of explaining the set of facts before us? Is there any other answer equally or more likely than cause and effect?"
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I think there are several things here. Can you leave it up there for a second?

Q. Sure.
A. He was mistaken on one point. He said cause -- he said none are sine qua non; none are necessary conditions. But of course cause has to precede effect. But he said the other eight, he said, look, these are guides, reminders, aspects, viewpoints for calling attention to things that we ought to review when we're looking at causation, but none of them is -none of them is a necessary condition. Moreover, when he goes through these individually, he provides a counter example to each one except for cause and effect. I don't know why he didn't pick up on that.
But moreover, if you look at the last sentence, "What they can do with greater or less strength is to help us make up our minds on the fundamental question" -- and this is that -- in the dashed statement there, is what I'm interested in -- "Is there any other way of explaining the set of facts before us? Is there any other answer equally or more likely than cause and effect?"

It does seem to me that his strategy here, if you will, his inferential strategy, is to make an inference to the best explanation for what's going on given the evidence. We've got one explanation; we have other possible explanations. What is the best explanation before us? Is there any other way of

explaining the set of facts before us? Is there any other answer equally or more likely than cause and effect? So he -as I read this last paragraph, he really is endorsing and utilizing what philosophers would call "inference to the best explanation."

Q. Now, this concept of all available information -- or information from different sources, I think is a better way to put it, maybe, or an easier way to put it -- with respect to National Toxicology Program, IARC, Bradford Hill, is it important to consider all the data?
A. Yes.
Q. So now what I want to do is I want to ask you a math question, since you have a background in math. Is there a recognized algorithm that exists that allows scientists to take all the available data on a substance regarding its carcinogenics and plug that data into an algorithm to conclude from a formula that A causes B or A doesn't cause B?
A. No, none that I know of. From time to time somebody will suggest they have one, but I haven't -- I don't think there's anything plausible there.
Q. All right. Now, you had mentioned something about scientific judgment?
A. That is correct.
Q. And we read this statement about scientific judgment being the basis upon which conclusions regarding carcinogenicity in

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humans or experimental animals are based on scientific judgment with consideration to all relevant information, correct?

A. Yes.
Q. All right. Now, what I want you to do, Dr. Cranor, is to talk about how often scientific judgment impacts the steps along the road to determining whether a substance causes cancer or not.
A. Okay. First of all, what you saw with respect to the National Toxicology Program, that they say in coming to your conclusion based on human evidence or animal evidence or combinations, in the final analysis you make a scientific judgment about what that shows. And there is similar language in the International Agency for Research on Cancer. In my book I quoted the director of the Monograph Series, Mr. Vincent James Cogilano, from an article that he utilized. And he used the same language.
Should I read that or just, you know -

Q. Is this out of your -A.
It's in the book, yeah.
Q. If you can just point me to the page in which -A.
Page 143.
Q. Where on this page?
A. Right at the top of the page, in the quotation marks.
So this -- first of all, let me say that this was taken from an article that he wrote called "Science and Practice."

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He wrote with several other IARC people about the procedures they use at IARC. Then he talks about how they use the stream of evidence from any human data they have, the stream of evidence that they have from animal data, and from that they get a kind of, you might say, preliminary judgment about what the causation is. And then they turn to other kinds of considerations, mechanistic evidence, genetic evidence that may add to that, modify it in some way.
But then he says, look: "The final overall evaluation by IARC is a matter of scientific judgment reflecting the weight of the evidence derived from studies in humans, studies in experimental animals and the mechanistic and other relevant data."

Q. All right. And -A.
And to answer your question, if you go to page 142, I went through various obvious places, it seems to me, that also scientific judgment enters in.
Q. And where do you want -A.
"The importance of scientific judgment" halfway down the page.
Q. Yes.
A. So beginning with the second sentence, "Inferences about causation typically rest on scientific judgment at several points. An expert reviews the data that appear to bear on causal judgments, selects scientifically relevant data, weighs
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the importance of different kinds of data vis-a-vis one another -- e.g., animal studies versus human studies versus short-term studies versus structure activity relationships versus even any case studies -- utilizes the studies that in her judgment are stronger and brings her background understanding of biology and toxicology, as well as her understanding of the phenomena, to the causal issues. She then evaluates different possible explanations in light of all the evidence and the phenomena, such as a disease, she wants to explain; that is, an expert integrates the scientifically relevant evidence in order to assess what it shows. Finally, expert judgment enters into an assessment of both the strength of the best explanation vis-a-vis alternative explanation."

And then it just goes on to quote a medical researcher and a person at the Federal Judicial Center. "In the final analysis, assessment of evidence and causal inferences depend on accumulating all potentially relevant evidence and making a subjective judgment on the strength of the evidence."

This is widespread. I mean, I quoted Cogilano and Kassirer and Joe Cecil and IARC and NTP, but you can just go on; lots of people agree with this.

Q. Okay. And now, on the subject of scientific judgment, can scientific judgment lead to scientific disagreement?
A. Yes. Two people may look at the same evidence and have a slightly different take on it.
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Q. And you cited a paper, I believe, as an example of this by Rudén?
A. Yes.
Q. And it is entitled "Interpretations of Primary Carcinogenicity Data in 29 Trichloroethylene Risk Assessments"?
A. Correct.
Q. And what I would like to do is -MR. JENSEN: It's Number 26 behind D in the notebook, your Honor.
BY MR. STEWART:

Q. What I would like to have you do, Dr. Cranor, rather than reading large portions of this paper -A. Sure.
Q. -- is to basically summarize what this author's attempting to do, and then I want to look at some of the things that she says in her paper and ask you to comment on them.
A. Sure. This is a philosopher, by the way, from Sweden. Let's see. What is her affiliation? It is the Royal Institute of Technology in Stockholm. I think if you look at it in Swedish, it's the King's Institute of Technology in Stockholm. She's a philosopher trained in toxicology and philosophy. What she did was to take 29 risk assessments, not by individuals but by some kind of committee of scientists, and look to see whether these risk assessments on the same subject -- and usually utilizing the same evidence for the toxicity, I think,
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and believe the carcinogenicity of trichloroethylene -- whether they agreed with one another and where they disagreed and why. She started with 29, but I think in a minute we'll talk about maybe seven that -- where they had really pretty much identical evidence but they still disagreed. These included organizations like the International Agency for Research on Cancer; they included the German Occupational Agency -- DFG, I believe is the synonym or the acronym they use there -- a group she labels IMM, which was a group of Swedish academics. The American Conference of Governmental Industrial Hygienists also looked at the issues. There was an industry group that I didn't write down the name; the acronym is HSIA. Let me see if I can spot what that is. The Halogenated Solvents Industry Alliance, Inc. Halogenated Solvents Industry.
An international European organization of the OECD, the

U.S. Public Health Service Agency for Toxic Substances and Disease Registry, and the subset of seven organizations looked at virtually identical human and animal evidence and gave its judgment about causal properties that TCE, trichloroethylene, might have.
Q. Okay. Now, what I would like to do is I would like to put up on the ELMO some of the statements in the summary and conclusions of this paper and just ask you to comment on them. This is at page 223 of the paper.
A. Okay.
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Q. Under "Summary and Conclusions" it says, "About one-fourth of the most cited primary carcinogenicity data (bioassays and epidemiologic studies) referred to in the TCE database have been interpreted differently by different risk assessors," meaning people were looking at the same data and coming to different conclusions, right?
A. Of course these were people looking at the same data and coming to different conclusions, but they were whole organizations; they were committees looking at the same data and coming to different conclusions.
Q. She goes on to say, "Seven risk assessors all face the same available epidemiological data. Three of them conclude that epidemiology is positive. However, these three risk assessors base their conclusions on different studies, reporting carcinogenic effects in different organs. One of them (IARC) motivates the conclusion with a meta-analysis of individually negative findings. Another motivates the conclusions by evaluating the quality of the study (Henschler, et al, 1995) differently than all of the TCE risk assessors. The third makes a cautious interpretation and extrapolation of uncertain data."
In summary, what's that trying to say?

A. She's saying that -- she's saying in general they looked at identical data -- or virtually identical data -- and came to different conclusions, and then she isolates later how little
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differences in judgment make a big difference in those overall conclusions.

Q. And then she actually goes on to say, "The other four risk assessors conclude that the TCE epidemiology is negative"?
A. Right. So three concluded it was positive; four concluded it was negative. All were doing perfectly respectable reasonable science, and they came to different conclusions.
Q. I want to just point out this last portion and ask you a question about it. It says up here, "This study provides examples of when and why risk assessors interpret toxicological data in different ways," right?
A. Correct.
Q. And in this study is there any mention of these folks wanting to have a predetermined outcome, and therefore bias, deciding that they know what the answer is beforehand and then biasing themselves to that?
A. No, I don't recall that she mentions anything like that. There were different committees taking up the issue and trying to decide what the science showed.
Q. Then she says here, "The differences in the interpretations of particular primary data, as presented by the TCE examples, may be small and seemingly insignificant. They are, for instance, all well within the scope of the scientifically acceptable interpretations. Yet, such seemingly, subtle differences have the potential to affect the
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overall risk assessment conclusions," meaning what?

A. Meaning that there are a lot of different judgment points in reviewing the data, and those judgment points, if they go one way, may well have a major effect on the overall conclusion; if they go another way, they may have a different major effect on the overall conclusion. And when you multiply these judgment cites, you see that it's quite possible to have substantially different conclusions even though the people are reviewing the same data and are perfectly respectable scientists within the ballpark where reasonable scientists would disagree.
Q. And we were talking about this 11th Report on Carcinogens. Benzene is in here, right?
A. What is?
Q. Benzene?
A. Benzene, yes.
Q. And it's under the category of "Known Human Carcinogen," correct?
A. Correct.
Q. And under that heading of "Known Human Carcinogen," what the National Toxicology Program has said about benzene is that the epidemiology studies are showing that benzene causes acute myelogenous leukemia in many, many studies, correct?
A. Yes.
Q. Does the National Toxicology Program say that benzene
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doesn't cause certain subtypes of AML?

A. I don't recall that they do. I'd have to review it. I don't think so.
Q. Now, in this case we asked you to -- just from a methodology standpoint of logic and reason from your background, your publishing, your reading, your participation in scientific advisory panels -- to just look at what Dr. Smith did, not to do his calculations for him, not to read the articles, but just to say was he reviewing the kinds of materials and taking into account the kinds of things that others not in litigation but who are agencies who try and determine does A cause B, does this substance cause cancer and can it, is it a probable human carcinogen -- was he considering those same kinds of information? And you did that?
A. Yes. He was considering generically the kinds of information that you would want a scientist to consider in arriving at their causal judgments.
Q.
All right.
MR. STEWART: One moment, your Honor.
(Pause.)
MR. STEWART: I'm going to pass the witness at this time.
MR. LEGHORN: Good morning, your Honor.
CROSS-EXAMINATION
BY MR. LEGHORN:

Q. Dr. Cranor, you've had a varied academic career; isn't that fair to say?
A. A very academic career?
Q. Varied. Various positions. You've been head of the phys ed department for a while, correct?
A. Yes.
Q. This -A.
Sorry to say.
Q. The Hispanic studies department?
A. Correct.
Q. History department?
A. Correct.
Q. Every once in a while you've used the term -- not with respect to your position, which is a distinguished professor, correct?
A. Correct.
Q. You talk about "distinguished groups of people." That's your opinion of that group, correct?
A. Yes.
Q. And it's your personal opinion, correct?
A. It is my personal opinion. I think I probably used that with respect to the International Agency for Research on Cancer and the National Toxicology Program. I think that if you did a survey, which I have not done, that you would find that's a fairly widespread view.
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Q. But your opinion -- your use of the word "distinguished" is your personal opinion today, correct? You haven't done that survey?
A. No, I have not.
Q. We've been talking about carcinogenicity, correct?
A. Correct.
Q. And carcinogenicity -- a substance is a carcinogen if it can cause any cancer in humans, correct?
A. IARC says that you have sufficient evidence for carcinogenicity if you have evidence that it can cause cancer in humans, correct.
Q. That's cancer in any organ, correct?
A. Correct.
Q. It could be in the bone marrow?
A. Correct.
Q. It could be in the skin?
A. Correct.
Q. And both would be -- if it only caused one of those, it would still be a carcinogen, correct?
A. Correct. Although they usually -- they make some attempt to indicate the variety of tumor locations that the substance has caused in animals or humans, but the older reports, I think, do that less than some of the current reports.
Q. Correct. But to become a known human carcinogen, a substance has to cause cancer in only one organ, correct?
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A. Well, to be a known human carcinogen?
Q. Known.
A. Perhaps. I'd have to -- but that's probably right.
That's certainly not true when it comes to animals because they typically cause -- they typically -- to use animal data you have tumor-causing agents that cause maybe in multiple species or maybe multiple sites or whatever.
Q. Often in animal studies -- and you're not a scientist, correct?
A. Correct. I have studied scientific inferences about causation, but I do not do animal studies.
Q. Right. Are you aware that oftentimes in animal studies you're using an animal that's susceptible to developing a number of cancers spontaneously?
A. In understanding what these agencies do, they review different kinds of animal studies. Sometimes they have particularly susceptible animals, and they usually try to take that into account. What is it, lung -- maybe lung tumors of certain mice are common.
Q. I'm sorry.
A. No, that's fine.
Q. Doctor, when something is a known human carcinogen, that doesn't mean it causes cancer in every organ in the body, correct?
A. That's correct.
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Q. And you mentioned that benzene is listed as a known human carcinogen, correct?
A. That's correct.
Q. And that does not mean that benzene causes cancer in every organ, correct?
A. That's correct.
Q. Or every form of cancer in a particular organ, correct?
A. That's probably correct; yes.
Q. Now -A.
But I think if you look at some of the studies you'll find, I believe, the study that -- the material that Mr. Stewart indicated suggests that benzene causes tumors all over animal bodies, and so it's a pretty potent cancer.
Q. It's also a known human carcinogen, correct?
A. That's correct.
Q. And it doesn't cause all forms of human cancer, correct?
A. That's correct.
Q. In fact, there isn't any evidence that it causes all forms of leukemia, correct?
A. I think that's the -- at issue in this case. I think there would be scientific disagreement about that. But I don't believe that IARC probably says something like that. It does say that benzene causes acute myologic leukemia.
Q. And you also talked about possible or probable human carcinogens, correct?
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A. Those are two different categories; yes.
Q. Okay. Let's focus on the probable. That's where you say that it could be based upon animal data?
A. Correct.
Q. Insufficient human data?
A. About whom are we discussing?
Q. Any probable human carcinogens. There's not sufficient human data?
A. At IARC?
Q. At IARC.
A. At IARC. That is correct.
Q. And you also say one of the things that keeps a substance in that category may be that you can't rule out observational biases, correct?
A. Can you rephrase that question? It was the way it was put.
Q. I believe your testimony was that a substance is often in the probable carcinogen category because you can't rule out that it's more -- that the alternative explanation -- to a reasonable degree of scientific certainty it cannot be ruled out. I believe that was your testimony.
A. I believe that was my testimony. That was the text we were looking at from the National Toxicology Program.
Q. And the mere fact -- and because that is the standard, it is equally likely that an alternative explanation is possible
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rather than exposure to that particular agent, correct?

A. I'm not sure that's quite right. You have human studies that -- they have different ways of describing that category. I believe one phrase is that a causal relationship is credible, but alternative explanations in the form of chance, confounding or some kind of bias in the study can't be ruled out with sufficient scientific certainty. I'm not sure that that means that it's equally plausible or equally possible; it's a possible explanation that they couldn't rule out.
Q. And it's a chance -- whether the results you are seeing occurs by chance is important; isn't that correct?
A. That was one of their categories.
Q. One of their categories.
And scientists test convention to rule out chance when looking at data sets, correct?

A. There are views about that, but there is disagreement about what that convention is and how you should best approach it.
Q. And you mentioned that -- you talked about IARC and the National Toxicology Board are interested in the public health, correct, protecting the public health?
A. They're interested in identifying substances that could pose harm to the public.
Q. Okay. I'll take that. But you're not trained in public health, are you?
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A. Do I have a degree in it? No.
Q. And -A.
But perhaps I should add that I was selected to be part of the Collegium Ramazzini because of the work that I had done and the contributions that could make to the public health. But I don't have an MPH or anything like that.
Q. And you've not studied it formally, correct?
A. I'm sorry?
Q. You've not studied public health formally, correct?
A. That's correct.
Q. And you have not studied epidemiology in any forum either, have you?
A. No, I have not.
Q. When Mr. Stewart was reading to you from the IARC publications, you said you didn't understand the term "clinical studies"; is that correct?
A. I wasn't quite sure what "clinical studies" meant. It might mean a full-blown clinical trial or it might mean something much less.
Q. But you said you were very familiar with that document, correct, and you would talk to people about it, correct?
A. Correct.
Q. And based upon that, you still didn't understand what they were saying -- what they meant by "clinical trials," correct?
A. I think I haven't looked at that sufficiently recently to

chase the footnotes down to see what that meant.

Q. One of the other things that you talk about, especially with the Rudén study, is that those folks there considered all of the evidence, correct?
A. That's correct.
Q. And it's important for a scientist to look at all the evidence, correct?
A. Correct.
Q. And that includes evidence that supports the hypothesis, correct?
A. Well, I'm not sure that that's how you begin. You look at the studies, and then you review the studies to see if they're going to provide relevant evidence, and then you decide what weight to ascribe to them and so forth.
Q. Okay. Well, you understand what the proposition that we're exploring here does: Exposure to benzene causes APL; is that right?
A. Yes.
Q. And if you wanted to explore that proposition, you would look at all of the relevant evidence, correct?
A. All of the -- that's correct. All the generically relevant evidence, and then you would review the studies.
Q. And is it proper to give no weight to studies or evidence that contradicts the hypothesis?
A. It -- I suppose you would say you would give weight to the

evidence that contradicts the hypothesis, but you have to be very careful about whether, in fact, the evidence does contradict the hypothesis.

Q. You'd want to investigate that data to see if it really is a problem with regard to the hypothesis, right?
A. You would want to review it.
Q. And similarly, with data that supports the hypothesis, you would want to make the same type of inquiry, correct?
A. I wouldn't, but a scientist would.
Q. A scientist would. But you're giving your opinions about what a scientist should do, correct?
A. Correct.
Q. So it would be fair to say that, in your opinion, a good scientist would get behind and look at the data to make sure that, in fact, it supports the conclusion, correct?
A. We would review it to see not necessarily whether it supports but whether it's relevant to making a difference in drawing the conclusion about which he's concerned. Some evidence will be relevant in support; some evidence may be relevant that doesn't support, although that's much -- that may be much more difficult.
Q. Much more difficult to assess that?
A. No, much more difficult to know whether it undermines it. Suppose -- suppose you have a hypothesis that there are germs on the desk here, and I come along and say, "Well, you know,

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Mr. Leghorn, I don't see any germs here," so that contradicts your hypothesis. Well, that would be a mistaken inference. My tools, my -- the power of my instrument for detecting germs are simply inadequate for providing evidence that contradicts your hypothesis.

Q. So you need to get the right tools for the job, so to speak, correct?
A. Correct. And you have to be careful how you use the tool.
Q. Correct.
And let's talk about that, because we talked a little bit about the Hill criteria. You talked about that none of them are important. And you also -

A. No, I didn't say that.
Q. None of them are essential?
A. None of them are a necessary condition for drawing a conclusion about causation -Q.
And -A.
-- except for cause precedes the effect.
Q. There's one thing, though, when you look at the criteria. Among the criteria listed here is none of them -- none of them says "association," right? The first criteria is strength of association, correct?
A. Correct.
Q. And it's there where Sir Bradford Hill talks about Dr. Snow's investigation into the development of disease in various
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neighborhoods in London, correct?

A. Correct.
Q. And in there he -- Dr. Snow -- looked at a number of households using different wells to see if the well in some way was contributing to the illness in certain households, correct?
A. That's correct.
Q. And with regard to one well, he found that the rate was 71 illnesses over ten in each -- 10,000 households, right?
A. I don't remember the particular figures.
Q. Well, it's right there, looking at page 8.
A. There it is. 10,000 households.
Q. And in another well, it was five per 10,000 households, correct?
A. Correct.
Q. And Dr. Snow is viewed as the father of epidemiology, isn't he?
A. That's probably correct. I'm not a historian of epidemiology.
Q. Okay. And the difference in the rate between those two households was 14 times, right?
A. Correct.
Q. And when Bradford Hill is talking there, he's saying, you know, when you look at the numbers, they're not big in terms of the 10,000 households, but the difference is big, right? He's talking about the strength of association?
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A.
The ratio, correct.
Q.
The ratio; the strength of association.
And here you have 14 times?
A.
Correct.
Q. And that would be viewed as a very strong association, right?
A.
I think that's correct.
Q. And when you get down to differences -- and probably here he didn't at the time do statistical tests, but you wouldn't need to do a statistical test to see if a rate like that was probably giving you true information, correct?
A. I don't know whether you'd have to do a statistical test or not, but that's pretty striking evidence.
Q. But when you look at potential rates of difference of 1.4 times, that's a weak -A.
That's certainly a lesser relative risk. I believe you will find that there's pretty widespread agreement that the -I believe it's lung cancer risks from secondhand smoke is slightly less than that, but it's a real causal relationship as far as people are concerned.
Q. And one of the reasons that people believe that is because statistical tests have been done to show that that's not a product of chance, correct?
A.
Probably that's correct, yes.
Q.
And that it's been -- that study and those -- that
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observation has been repeated a number of times, correct, in different -

A. I don't know the details, but I suspect that's correct.
Q. Now, in the study that you talked about with Rudén, you said that -- you're familiar with the study, correct?
A. Yes.
Q. That everybody here was looking at the same data with regard to carcinogenicity, correct?
A. Correct.
Q. And that's just causing cancer -- a cancer in a human, correct?
A. Probably a type of cancer.
Q. But it could be a -- it could be a carcinogen if it caused a cancer, correct?
A. Correct.
Q. And the studies that were looked at here were evaluated for their outcomes, correct?
A. Correct.
Q. Their statistical significance, correct?
A. They did use human epi studies and presumably they did look at that.
Q. Well, you reviewed this paper for your -- in preparation for your report, correct?
A. Correct.
Q. And you're aware that study -- there were some studies

that were positive, correct?

A. Correct.
Q. There were some studies that were inconclusive, correct?
A. Correct.
Q. There were some studies that were negative, correct?
A. Uh-huh.
Q. Yes?
A. Uh-huh.
Q. Yes?
A. Yes.
Q. The court reporter can only take down what we say.
A. Sorry.
Q. And there were some studies that weren't statistically significant, correct?
A. I don't recall, but that may be the case.
Q. Why don't you take a look at Table 4. A number of those studies shows p-value greater than .05, correct?
A. Yes.
Q. In fact, there they -- some of them are .29, correct?
A. Yes, that's correct.
Q. And a p-value of .29 would mean it has a one-in-three chance of being the product of chance, correct?
A. That's correct. That means if you did the study 100 times, 70 percent of the time it would turn out as this study turned out, and 30 percent of the time it would be mistaken on

the grounds of chance.

Q. And that's not accepted in the scientific community as statistically significant, correct?
A. Well, I'd cautioned about that claim earlier. The scientists with whom I work and discuss things do take seriously the idea of -- well, they take more or less seriously the idea of statistical significance, but they don't necessarily take seriously the idea of a particular value for statistical significance. They say you've got to understand what your data shows. If it has a 10 percent chance of being mistaken as a result of chance, that's -- you just factor that in. It doesn't have to be a 5 percent chance.
Q. This is a one-in-three chance, correct?
A. This is a one-in-three chance.
Q. Thirty-three percent?
A. Correct.
Q. Or 30 percent chance?
A. Right.
Q. And having an effect also depends on the decision you're making, correct?
A. It might. But I think you would want to see what other evidence you had. And this might add to the other evidence you had or it might subtract from it. I don't know.
Q. Certainly, Doctor. What I'm saying is that the proposition with IARC, which you say is to protect the public

health, we may use a standard for avoidance, correct? The question is: Can we reduce the risk to the exposed public, correct?

A. No. They're not a regulatory agency; they're an agency that tries to identify cancers, and they leave it to national governments what to do with their evidence.
Q. Right. But the evidence is used to reduce the risk in the population of exposure to agents, correct?
A. I'm not sure that's correct. The evidence is used to identify substances that are carcinogens, and then they tell the world, as it were, that these substances are carcinogens and leave it to those communities what to do about it.
Q. All right. And they have "known" and "probable" as we've gone through?
A. Correct. Correct.
Q. And an agency might decide that, in the interest of public health, if it's a probable, it's something that maybe we should avoid even though we're not certain, correct? They're making a regulatory decision to protect the public health?
A. A community might. But that's a pretty strong statement. They're saying it's more likely than not that this is a human carcinogen and -- so I think it's not quite the way you put it.
Q. And is protecting the public health the same as imposing liability for exposure?
A. I believe that the causal inquiry as to whether something

can produce a cancer is a similar process of reasoning.

Q. Similar process of reasoning but different standards may apply, correct?
A. They may, but they may not.
Q. It's your position that they should not, correct, in your writings?
A. I'm not sure that I've said that directly. For example, when I served on the Electromagnetic Fields Panel of the State of California, they noted in there that very often regulatory agencies adopted a standard of proof, as it were, that has to be satisfied before they issue regulations that the committee called "beyond a reasonable doubt." So that's actually a very high standard of proof. The standard of proof that you utilize depends on the venue in which you're working and what you seek to cause -- seek to do.
Q. Now, Doctor, here we're really evaluating methodology, aren't we, whether the methods that Dr. Smith used meet the Daubert standard, correct?
A. That's not my task.
Q. Okay. You've been critical of the Daubert standard, isn't that correct, in your writings?
A. I have done some writing about how -- not necessarily the Daubert standard, but how sometimes it gets used.
Q. And you've been critical of how it's been used, correct?
A. Sometimes, correct.
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Q. And -A.
But that's not my job here today.
Q. Correct.
Now, Doctor, you sat here and you talked about you've reviewed Dr. Smith's report, correct?

A. I've read his report.
Q. You didn't see that -- you didn't make any inquiry as to whether he, in fact, reviewed all of the relevant evidence, correct?
A. No, I did not. He reviewed and discussed the generic kinds of evidence that you would expect someone in that position to do.
Q. And when you come to say that people might disagree looking at the same evidence, you made no inquiry here as to whether Dr. Smith looked at the same evidence that anyone else did, correct?
A. No, I did not make that inquiry.
Q. And you -A.
I'm interested in a kind of a pattern of reasoning. Did he engage in the form of reasoning that scientists in other contexts, as exemplified by the National Toxicology Program, the International Agency for Research on Cancer, have done?
Q. And you made no assessment as to whether his statements about what studies said were, in fact, true?
A. I did not inquire into that.
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Q. You didn't get behind any of his calculations that you saw yesterday, did you?
A. I couldn't see all of them, but, no, I did not.
Q. Well, you heard them, didn't you?
A. Yes.
Q. In fact, you didn't pick any of his calculations, so it wouldn't matter if you saw them; right? Is that correct, sir?
A. I read some of the calculations in support, but I did not dwell on them; that's correct.
Q. And in the form of reason that you talk about, sometimes if the data on which you rely is wrong, you'd come to a wrong conclusion, correct?
A. That's likely correct, although when you have an inference to the best explanation, you don't have such a tight connection between mistakes somewhere in your premises, as it were, and necessarily a mistake in your conclusions.
Q. But the -A.
Because you're relying on a whole body of evidence.
Q. So you have to look at how many times there may be errors or mistakes to see what the probability would be if the conclusion isn't there, correct?
A. Correct. But also to see whether those differences in data analysis were differences that reasonable scientists could disagree about. Is that within the realm of scientific judgment? It seems to me that that's something that one has to
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assess.

Q. And when you look at that, you offer no conclusion -opinion here that Dr. Smith's conclusion is right or wrong, correct?
A. That is correct. He just -- I'm looking to see, you know, that the form of the argument, is he engaging in the issues and has he considered the generic kinds of evidence that scientists exemplified by NTP and IARC would do, and the answer is yes.
Q. And it's a formalistic inquiry, not a substantive inquiry that you've made?
A. I think we've discussed this in deposition. "Formalistic" may be slightly strong, but I was looking at the form of the argument, the evidence patterns, the kinds of evidence considered. I would balk a little at the word "formalistic."
Q. But you looked at the form of argument, correct?
A. Yes, I did.
Q. And yesterday you were here, right?
A. Yes.
Q. And you were here for all of Dr. Smith's testimony?
A. Yes, I was.
Q. And I talked to Dr. Smith about his inclusion of some data in some calculation he made here, correct?
A. You had that discussion with him, correct.
Q. And he said that he used different inclusion data in his medical articles from his testimony in court. Is that
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something a reasonably prudent scientist would do?

A. I think it depends on how it happened. I think sometimes people forget things or, you know, don't put in things earlier. I don't know about further colloquy about that point.
Q. If you were to assume that that was one of the articles that was cited and relied upon -- or both of the articles were cited upon and relied upon in his report, would that make a difference to you as to whether that's something a prudent scientist would do?
A. I think I would like that question rephrased. In a sense you have two papers that cite different -- slightly different data -Q.
Well, Doctor -A.
I've forgotten enough of the discussion. You'll have to remind me.
Q. In the Golomb paper, for the purposes of his testimony here, Dr. Smith made some assumptions among 16 cases as to who were probably or likely exposed to benzene, okay?
A. Okay.
Q. And in a paper that he published, he looked at that same paper, Golomb, and selected from those 16 a different eight as being -A.
A totally different eight?
Q. Two out of the eight.
A. Were different?
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Q.
Were different.
And I asked him here, "Did you apply different criteria?"
And he said, "Yes."
Is that something a good scientist would do in offering an opinion on cancer causation?

A. I don't know. I think I would need to know more about the context in which that -- you know, in which that occurred. It's only one piece of evidence. It's, I think, not the full body of evidence. And so you might say, "Well, let's throw out that piece of evidence." Now, does that make any difference to the overall conclusion? It may not.
Q. Okay. So we would -- to explore whether Dr. Smith's conclusion is one that was correctly reached now, because of this suspicion you would throw that data out?
A.
No, I didn't say that. That would be -Q.
Well, excuse me. You would throw that data out and see if the conclusion could still be maintained?
A. One would want to review the body of data, perhaps with one of those papers, with the other paper, maybe neither, and then see what -- how that influenced the conclusion. I suspect that -- you know, ordinarily in scientific inferences you're considering a large body of evidence, and a single piece is not determinative in that respect.
Q. And one would have to look to see how important that piece of data was in coming to the conclusion offered here, right?
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A.
You would want to talk to Dr. Smith about that.
MR. LEGHORN: No further questions, your Honor.
THE COURT: Mr. Stewart?
MR. STEWART: Yes. Thank you, your Honor.
REDIRECT EXAMINATION
BY MR. STEWART:

Q. Dr. Cranor, I want to go back to the Bradford Hill paper because I want to read from page 8. You were asked about John Snow?
A. Yes.
Q. Yes? All right.
I want to read the part right after that discussion, John Snow, page 8, and ask you a question about it. It says -after discussing that John Snow portion that Mr. Leghorn put up on the board, it says, "In thus putting emphasis upon the strength of an association we must, nevertheless, look at the obverse of the coin. We must not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears to be slight. There are many occasions in medicine when this is, in truth, so. Relatively few persons harboring the meningococcus fall sick of meningococcal meninginitis. Relatively few persons occupationally exposed to rats' urine contract Weill's disease."

When he says "the obverse of the coin," what's he

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addressing?

A. He's saying, first, this is a consideration that might help us come to a causal conclusion, but are there circumstances where you might not have it and where this consideration would not be relevant? And that's what -- he, in effect, provides something like a countereffect, as philosophers would put it here. And he does this for all of his considerations. He says, "This is what you look at, but there may be circumstances where you don't have it."
Q. And Mr. Leghorn also asked you about statistical power or test of significance; do you recall that?
A. Correct.
Q. I want to read what Dr. Hill said about test of significance.
A. I almost read that the first time around, I suspect.
Q. Dr. Hill said under the heading "Tests of Significance," his first sentence says, "No formal tests of significance can answer those questions."
In fact, in this article, Dr. Hill is quite critical of the formulaic test of significance, isn't he?

A. Yes, he is. And if you look at the column that's just out of sight on your scene on the right, he accuses the United States -- researchers in the United States of being too enamored with too many tests of significance.
Q. Right. He says, "I wonder whether the pendulum has not
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swung too far, not only with the attentive pupils but even with the statisticians themselves. To decline to draw conclusions without standard of error can surely be just as silly. Fortunately, I believe we have not yet gone so far as our friends in the USA where I'm told some editors of journals will return an article because tests of significance have not been applied."
That's what you're referencing; is that right?

A. That's what I'm referencing, yes.
Q. And then he says this: He says, "Too often I suspect we waste a deal of time, we grasp the shadow and lose the substance, we weaken our capacity to interpret data and to take reasonable decisions whatever the value of P, and far too often we deduce no difference from no significant difference." What does that mean?
A. Well, he's suggesting that we can utilize formalistic, as it were, tests to the detriment of paying attention to what the body -- what the evidence itself really shows even if they don't fully satisfy a particular formalistic test of the evidence.
Q. Okay. Now, you were asked some questions by Mr. Leghorn about whether or not what these -- what the National Toxicology Program or IARC were doing was actually just trying to find out if something was a carcinogen that was in any organ and it got listed as a cancer-causing agent; do you recall that?
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A. Yes, I do.
Q. And you said something about generally what takes place is they will provide information about what is found and what cancers that they are relating to certain kinds of substances, true?
A. That is correct. They provide -- they provide some degree of detail, and more recently, I think.
Q. Yes. So this is what I would like to do. I would like to read from the 11th Report on Carcinogens, 2004, page 3-26. Since this is a case about benzene, let's read specifically what the National Toxicology Program in 2004 says about benzene. It says, "Benzene: Known to be a human carcinogen. First listed in the First Annual Report on Carcinogens, 1980." So the first time this report came out, benzene was a known carcinogen, correct?

A. That's correct.
Q. It says, "Carcinogenicity: Benzene is known to be a human carcinogen based on sufficient evidence in humans. Case reports and case series have reported leukemia (mostly acute myelogenous leukemia, also known as acute myeloid or myelocytic leukemia) in individuals exposed to benzene. The strongest epidemiologic evidence that benzene causes cancer is from several cohort studies in various industries and geographical locations which found that occupational exposure to benzene increased the risk of mortality from leukemia (mainly acute
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myelogenous leukemia.) Case control studies also reported that exposure to benzene increased the risk of leukemia, but the usefulness of these studies was limited by poorly defined exposures and mixed exposure patterns," citing IARC 1982 and 1987.
It goes on to say, "Since benzene was reviewed for listing in the First Annual Report on Carcinogens and by the International Agency for Research on Cancer, numerous epidemiological studies of benzene exposure have been published. Some studies found that the risk of leukemia increased with increasing benzene exposure; increased risk of death from leukemia was very high in the groups with the highest exposure." IPCS 1993 is the cite.
"Savitz and Andrews, 1997, reviewed 18 community-based and 16 industry-based studies of benzene exposure and suggested that the evidence supported an association between benzene exposure and leukemia in general, rather than specifically with acute myelogenous leukemia." Let me just stop right there. Mr. Leghorn said something about this issue. Aren't we seeing here in the National Toxicology Program them listing what the studies are showing, that benzene is causing lots of different kinds of -

A. They're showing it's causing several different types of diseases here, yes, not just a single type.
Q. "Most studies found that benzene exposure increased the

risks of total lymphatic and hematopoietic cancer; i.e., cancers of the lymphatic system and of organs and tissues involved in production of blood. Total leukemia" -- that would include APL?

A. APL, yes.
Q. -- "and specific histologic types of leukemia, including chronic lymphocytic leukemia, as well as acute myelogenous leukemia." It then says, "Little evidence was found for an association between benzene exposure and multiple myeloma or non-Hodgkin's lymphoma," correct?
A. Correct.
Q. So when they found little evidence of something, they said it, correct?
A. They said it.
Q. Let's keep going. "The evidence in humans is supported by studies in experimental animals including many published after benzene was first reviewed for listing, demonstrating that benzene causes cancer at multiple tissue sites in rodents. Benzene was tested for carcinogenicity in mice and rats exposed by several routes, including oral administration, inhalation, injection and dermal application.
"When administered orally, benzene caused Zymbal-gland carcinoma and oral cavity tumors in rats of both sexes, skin carcinoma in male rats, Zymbal-gland carcinomas, malignant lymphoma and lung tumors in mice of both sexes; harderian-gland

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adenoma and preputial-gland carcinoma in male mice and ovarian tumors and mammary-gland carcinoma and carcinoma sarcoma in female mice (NTP 1986).
"When administered by inhalation, benzene caused tumors at many tissues sites in rats and a tendency towards lymphoid tumor induction in mice. Benzene administered by intraperitoneal injection caused benign lung tumors in male mice. No tumors were observed in mice administered benzene by subcutaneous injection or dermal application," citing IARC 1982 and 1987.
"However, dermal applications of benzene caused benign skin tumors in transgenic mice carrying the v-Ha-ras oncogene, which increases their susceptibility to carcinogens."
This is an example of you knowing that when they're using a mouse or animal that might be predisposed to it, they so note it, right?

A. They typically note it. This is a typically susceptible model for testing that substance.
Q. For that one?
A. For that one.
Q. And they cite Blanchard, et al, 1998; Spalding, et al, 1999; and French and Saulnier 2000.
"Later studies reported that when administered benzene by gavage, heterozygous p53 deficient mice (with only one functional copy of the p53 tumor-suppressor gene)" -

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A. Can you raise it again? Thank you.
Q. Thank you.
A. Thank you.
Q. -- "developed head and neck, thoracic cavity and subcutaneous carcinomas," listing French, et al, 2001, and Hulla, et al, 2001, correct?
A. Correct.
Q. So -A.
I think during cross-examination I referred generically to this detail of tumors found in the animal studies in particular, and there's some variation in the tumors found in humans as well.
Q. Yes. And so, Dr. Cranor, from that extensive report that NTP has in its most recent Report on Carcinogens in 2004, if the National Toxicology Program believed that benzene didn't cause APL, they could have put it in there, right?
A. They could have put it in there.
Q. And they didn't, right?
A.
Didn't see it.
MR. STEWART: Thank you.
THE COURT: Anything else?
MR. LEGHORN: I have a few questions.
RECROSS-EXAMINATION
BY MR. LEGHORN:

Q. Doctor, you were asked a question about total lymphatic

and myelogenous cancer, correct, the phrase?

A. I believe that was one phrase used.
Q. When you said -- when you were thinking about that, were you reading "total" as all or total number of cases?
A. I don't know that I'd phrase that distinction.
Q. I understand that. But when you answered the question "yes," what did you understand the question to be?
A. Would you rephrase your choice so that I may make sure that I may make -Q.
When you were asked the question that benzene exposure increased total lymphatic and myelogenous cancer -A.
Okay.
Q.
-- you said that you agreed with that?
MR. STEWART: Hold on. I object to that. I didn't ask that.
THE COURT: You should use the text to get the way the question was answered.
MR. STEWART: Yes. Would you like the text?
MR. LEGHORN: Yes.
THE WITNESS: I agreed that they said it.

BY MR. LEGHORN:

Q. Oh, you agreed that they said it?
A. Right.
Q. But you don't know what they were saying?
MR. STEWART: Well, let's use the text because what

you said I said, I didn't say.
MR. LEGHORN: Your Honor, may we address the Court?
THE COURT: Well, no.
MR. LEGHORN: You mean, just -- I mean, rather than

the colloquy, I'll ask the question?
THE COURT: That's right. Mr. Leghorn's questioning,

but now use the text.
MR. LEGHORN: Correct.
THE COURT: Okay.

MR. STEWART: Thank you.
MR. LEGHORN: I'll read it from here.
MR. STEWART: Well, I kind of want to make sure you read it all.
MR. LEGHORN: Your Honor, I've never had counsel remind me -

THE COURT: Go ahead.

MR. LEGHORN: Thank you, your Honor.
BY MR. LEGHORN:

Q. The sentence which includes "Most studies found benzene exposure increased the total" -- "the risk of total lymphatic and hemapoietic cancer -- i.e., cancers of the lymphatic system and of organs and tissues involved in the production of blood -- total leukemia and specific histological types of leukemia, including chronic lymphocytic leukemia as well as acute myelogenous leukemia."
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What was your understanding of that, or did you simply say that was what was written there?

A. That's what was written. I think there may be some ambiguity, but you would want to look at it. I was not offering my interpretation of what IARC said, or NTP said.
Q. That's fine. That's what I wanted to clear up, that you were simply saying that's what was written there.
And, Doctor, do you remember at your deposition you and I discussed the null set, correct? That's proving the nonexistence of something, correct?

A. We had a substantial problem there. I take the words "the null set," in set theory, as not something that you can show; it's an axiom of set theory. That's different from the null hypothesis.
Q. I come from the more math side than you do. So we had this. So let's go to the null hypothesis -A.
Okay.
Q. -- so we're talking the same language. I apologize.
A. Yeah.
Q. Doctor, you can't prove the null hypothesis, correct, with inferential reasoning?
A.
That's commonly said by the scientific community, correct.
MR. LEGHORN: No further questions.
THE COURT: Okay. All right, Dr. Cranor. Thank you.
You may step down.

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(The witness is excused.)

THE COURT: We'll take the morning recess.

THE CLERK: All rise.

The Court will take the morning recess.

(There is a recess in the proceedings from 11:23 a.m. to 11:45 a.m.)

THE CLERK: All rise.

The continuation of the Milward hearing.

Please be seated.

THE COURT: Does that complete the plaintiffs' witnesses?

MR. STEWART: Yes, your Honor. Those are our two witnesses.

THE COURT: Okay.

MR. LEGHORN: Your Honor, at this time we'll call Dr. David Garabrant.

THE COURT: Okay. I'd appreciate it if you would use the podium.

MR. LEGHORN: Can I move the podium?

THE CLERK: No.

THE COURT: Okay. Never mind. I'd like you to use the podium. I'd prefer if you'd use it in the future.

MR. LEGHORN: I just need to unplug it and then move it.

THE COURT: Okay. If that's all there is. I just

don't want to cause a technical glitch.

MR. LEGHORN: No.

THE COURT: Okay. Dr. Garabrant?

MR. LEGHORN: Dr. Garabrant, if you would please take the stand.

THE CLERK: Step up to the box, please.

DAVID HAY GARABRANT, sworn

THE CLERK: Please be seated. State your name, spell your last name for the record, keep your voice up and speak into the mic.

THE WITNESS: David Hay Garabrant, G-A-R-A-B-R-A-N-T.

MR. LEGHORN: Do you have it, your Honor?

THE COURT: I'm sorry. Do you want to -

MR. LEGHORN: Yeah. Yes, your Honor.

I've got it. Thank you, your Honor.

DIRECT EXAMINATION
BY MR. LEGHORN:

Q. Dr. Garabrant, can you please state your full name and address for the record.
A. David Hay Garabrant, 1420 Washington Heights, Ann Arbor, Michigan 48109.
Q. Dr. Garabrant, can you please describe your educational background.
A. Yes. I received my undergraduate degree in chemical engineering, magna cum laude, from Tufts University; I received
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my M.D. degree from Tufts University School of Medicine, not too far from here; I received a master of public health from the Harvard School of Public Health; and I received a master of science in physiology also from the Harvard School of Public Health.

Q. Was your degree in physiology in any particular specialty?
A. It was from the Department of Physiology, but it was focused on occupational health and chemicals and their effects on human health.
Q. Doctor, you indicated that you are -- that you received an M.D. degree, correct?
A. Yes.
Q. Are you licensed to practice medicine?
A. I am.
Q. And where are you licensed?
A. I have an active license in Michigan; I have inactive licenses in Massachusetts, Washington, D.C., Maryland and California.
Q. And, Doctor, are you board certified?
A. I'm board certified in internal medicine and also in preventative medicine with specialty certification in occupational medicine as part of preventative medicine.
Q. Doctor, can you -- you indicated that you have degrees in public health, correct?
A. Yes.
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Q. Can you describe the discipline of public health, the academic discipline?
A. Public health is the area that seeks broadly to maintain the health of populations. When I went to public health school, some of the faculty quipped that medicine is a discipline within public health because medicine focuses on the treatment -- the diagnosis and treatment of illness, whereas public health focuses more broadly on disease prevention, nutrition, behaviors that lead to unhealthy habits, occupational health, which is the area that I've spent my career in, international health, vaccination programs, disease screening. And so the overall theme of public health is to try to protect the health of populations, and it includes caring for the sick.
Q. Doctor, you've held some teaching positions; is that right?
A. Yes.
Q. Can you describe them generally?
A. When I finished my residency training I took a position as assistant professor of medicine at the University of Southern California School of Medicine. I was tenured there in 1988 and then moved to the University of Michigan to lead the occupational medicine program. At Michigan, I was associate professor and then promoted to full professor. In that role I have been the director of the Occupational Medicine Program,
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director of the Occupational Health Program, the director for the Center for Occupational Health and Safety Engineering, director of the Cancer Prevention Training Program and founding director of the Risk Science Centers. So I've had a series of administrative-type positions in addition to being a full professor.
In the fall of 2007, I took emeritus status in the regents of the University of Michigan, granted the title of Emeritus Professor of Occupational Medicine and Epidemiology. I also was professor of epidemiology for quite a number of years.

Q. And would you describe yourself as an epidemiologist?
A. Yes.
Q. What does that mean?
A. It means that I have spent my career designing, conducting, analyzing and reporting the results of epidemiology studies; it means I've taught epidemiology; it means I've published in the area of epidemiology.
Q. Doctor, have you received any grants from the CDC or NIOSH or any other governmental agency?
A. Yes. I've received grants from the National Institute of Health, National Institute for Environmental Health Sciences, the National Institute for Occupational Health and Safety, the State of California, the American Cancer Society, the United Auto Workers, Ford Motor Company, National Joint Committee on Health and Safety, the Dow Chemical Company, the Romanus

Corporation (ph). I could go on for a while.

Q. In connection with the government grants, do you recall any of the subject matter of your studies?
A. Let's see. We've done grants looking at causes of pancreas cancer, grants looking at causes of breast cancer. There are lots more I could talk about.
Q. In terms of courses that you have taught, what courses have you taught as a professor?
A. The two major courses throughout my career have been occupational diseases, which focuses on the various chemicals and physical agents and activities in the work environment that pose a risk to health; and the other is research methods in occupational epidemiology, which is teaching graduate students how to design and conduct epidemiology studies of populations of workers and people exposed to chemicals and workplace exposures.
Q. And, Doctor, in the course of teaching, did you scientists have a methodology for addressing questions of cause and effect?
A. Yes.
Q. Could you explain that to us, what this is?
A. Yeah. In epidemiology we use the scientific method that is customary in every branch of science which essentially follows the sequence of steps. We start with a hypothesis. Sometimes this comes from case reports, but it's essentially,
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gee, I've got an idea that A causes B, or drinking coffee causes pancreas cancer. We then design a scientific study that is intended to provide a test of that hypothesis. The study has a protocol: It involves collecting data; it involves having a control or comparison group.
After we've collected the data, we analyze the data using various data management and statistical methods software. And then we try to interpret what those analyses say to decide whether the data supports the hypothesis or does not support the hypothesis.

Q. Doctor, why -- you say that -- on your slide, the importance of controlled studies. Why are controlled studies important?
A. Well, a controlled study refers to an idea -- if you're going to look at whether a series of factors are associated with some outcome, you cannot do that in a manner that's interpretable without having a comparison group. And so the easiest analogy is a laboratory experiment where you expose one group of animals to a chemical and you have a comparison group that's identical in every way but for exposure.
In the world of epidemiology, we don't get to design experiments very often, so we often look at, for example, a group of workers who have a shared exposure, a common exposure, and compare them to a group of workers who do not have that exposure but who are as similar as possible in every other way.

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Q. Is that to isolate an independent variable, Doctor?
A. That is to try to be able to define the effective exposure and -- in order to minimize or eliminate the possibility of confounding by other causative factors.
Q. And after you look at the data, what are the possibilities, as a scientist?
A. Well, you have to make an interpretation of whether the data supports the hypothesis, in which case you say, yea, we're lucky this time or, conversely, whether it does not support the hypothesis. And typically not supporting the hypothesis comes in the form of finding no association between exposure and disease.
Q. And, Doctor, you've mentioned here the issue of forming a hypothesis. And you heard the testimony of Dr. Cranor when we discussed the null hypothesis. Can you describe what the null hypothesis is?
A. Yes. It's customary in science to use the term "null hypothesis" to refer to there being no association between exposure and outcome. So if I were using my example of coffee drinking and pancreas cancer, the null hypothesis would be that they have no association at all. And then the alternative would be to specify that they have some causal relationship. And then we test the alternative hypothesis.
We're almost -- most science now follows the concept of refutation advanced by Karl Popper, that you seek data that

tries to refute the hypothesis. And if the data supports the hypothesis, you say, "Ah-ha, we were unable to refute it. It may be true"; if the data does not support the hypothesis, you say, "We refuted it. There's not evidence that it is true."
So you go back, you form a new hypothesis, design a new study and start anew.

Q. And in your work in this case, what do you understand the hypothesis to be that was under investigation?
A. I believe the hypothesis is that benzene exposure causes acute promyelocytic leukemia, or APL.
Q. And have you, after review of the reports by Dr. Smith and listening to his testimony, formed an opinion as to whether the evidence is adequate to support the hypothesis that benzene causes acute promyelocytic leukemia?
A. I have.
Q. And what is that?
A. No, I have not seen evidence that supports that hypothesis, much less proves it.
Q. And how did you come about that opinion?
A. Okay. Well, let's start with this diagram. It's important to specify what disease we're talking about. And I believe we're talking about APL. We're not talking about other forms of AML. I don't think they're the issue. I would readily agree that benzene has been shown to cause AML in human epidemiology, but I don't think that's the issue here today,
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because APL is a distinct disease that has important defining characteristics. So the issue is APL.
Some of the literature looks at all leukemia. That's not the issue. Some of the literature looks at all lymphohematopoietic cancers. That's not the issue either.
Similarly, on the exposure side, the issue is benzene. We're not looking at solvents; we're not looking at workers in shoe factories, people who paint or work in printing factories; we're not looking at the effect of gasoline, diesel or petroleum or exhaust gases, even though some of those exposures may involve benzene or may result in exposures to benzene at low levels. The issue is whether benzene causes APL.

Q. And how does a -- how does an epidemiologist sort through the relevant evidence to explore the cause-and-effect hypothesis?
A. Well, you, first of all, have to state the hypothesis, and you have to state it clearly. It is: Does benzene cause APL? If you want to test any of the other hypotheses, you'd have to systematically assemble the evidence regarding those other hypotheses. As you can see in this diagram, there are -- I don't know -- three times five -- 15 other hypotheses. If you wanted to test any of those, you would have to systematically go out and gather the literature.
Now, for example, there is a very large literature that looks at motor fuels, gasoline and diesel, in relation to

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leukemia risks and AML risks and risks of all lymphohematopoietic cancer. We haven't assembled that literature today. And before we could invoke whether there is or is not a causal association, we'd have to assemble that body of data. And it's a big body of data.

Q. And, Doctor, before you go on, we've used the term, and we've heard it over the last several of days, yesterday and today, "epidemiology." Could you explain to us exactly what epidemiology is?
A. It is the scientific discipline that studies the patterns of diseases in human populations, and the patterns of exposures.
Q. And yesterday when I asked -- or I spoke with Dr. Smith about cohort studies. Can you explain to us what cohort studies are?
A. Yeah. A cohort study is a study in which you identify a population of people who have some exposure in common. We call that the exposed population, a cohort of people who are exposed. And you assemble a group of people who do not have that exposure. That is the reference group, or non-exposed group.
Q. Then what do you do?
A. One of the critical or defining elements of a cohort study is that you follow both groups over time to see who gets diseased. So the time element is essential to a cohort study
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because disease incidence occurs in a population as time passes.

Okay. So you watch the populations over time and then you compare the two groups to see which group has the higher rate of disease.

Q. Before you go on, Doctor, you mentioned there's a time function. Can cohort studies be retrospective, prospective or a combination of both?
A. What you're referring to is where the observer sits in relation to the occurrence of events. Yes, you can do a cohort study retrospectively, in other words, looking back at past events; you can do a cohort study looking prospectively, starting now and watching as events develop; you can do a combination of the two. So you can situate the observer anywhere in the timeline.
Q. And when you get the results from your cohort studies, what may you see?
A. Well, you can see that the two groups have equal rates of disease; you can see that the exposed group has a higher rate than the non-exposed group; you can see that the exposed group has a lower rate of disease than the non-exposed group.
Q. And if you see a group in a cohort study where there is the same?
A. Well, let me explain it. First off, we have to make sure that we include the time element. So let's assume that both of

these groups, these cohorts or populations, are followed for ten years. So there are 12 people in each population. So each group has 120 person years of observation. Okay. So among the exposed group we see that two cases have disease -- of disease have developed in 120 person years of observation, and in the non-exposed group two cases have occurred in 120 person years of observation.
We take the ratio of the rates in those two groups. So the rate in the exposed group divided by the rate in the non-exposed group, when they are the same, the ratio is 1.0. That means there is no association; the rates are identical.

Q. And what happens if the rate -- what can you draw from a rate that's increased in the exposed group?
A. Well, in this instance we see that the rate in the exposed group is four times the rate in the unexposed group. We would call that a positive association because the exposed group is at higher risk of disease by a factor of four.
Q. And if it is less in the exposed group?
A. And this is the inverse. Here the exposed group has one quarter the rate of the non-exposed group, and so we would say there is a negative association, meaning that the rate is lower in the exposed group by -- here, in this instance, by a factor of four.
Q. Earlier when we were talking about -- you were posing a hypothesis. If your hypothesis is exposure causes a particular

disease, what's the significance of a negative association?

A. Well, there are instances where negative associations can and should be interpreted that the exposure prevents the disease. If the exposure were wearing seatbelts, we would find that people who wore seatbelts had lower risks of motor vehicle fatalities than people who do not. So that you could have a preventative effect, an inverse causal relation.
Q. We also mentioned case control studies. Can you tell us about those?
THE COURT: Before you go on to that, can I ask a question about the cohort studies?

MR. LEGHORN: Sure.

THE COURT: The denominator you've been using in the ratio is person years?

THE WITNESS: Yes.

THE COURT: And in this example, in each cohort there were 12 persons measured over ten years. Can you use different numbers -- different factors to produce the same person years without affecting the relevance? For example, could you use 30 persons over four years to get to 120 person years and compare that to 12 persons over ten years, or would that produce problems?

THE WITNESS: Yes, you can do that. The time

structure and the size of the populations does not have to be the same. It's quite customary to have cohorts of different

sizes. Often, they are followed for the same period of time and during the same historic period.

THE COURT: In that case, you would have different person years in each ratio.

THE WITNESS: Sure. And that's why we calculate rates and compare the rates.

THE COURT: So the person years for each doesn't necessarily have to be the same?

THE WITNESS: That is correct.

THE COURT: And if it is the same, it doesn't have to be produced by the same factors?

THE WITNESS: That is correct.

THE COURT: A product of the same.

THE WITNESS: It could be a different number of people or a different duration to follow.

THE COURT: Are there any limits on that? In other words, would 120 people over one year make a difference?

THE WITNESS: In theory, no; in practice, you want to see that people were followed in the same historic period in case there are changes in the background rate of disease over time. So, for example, with a disease like AIDS, where there was no known AIDS and then it took off, you don't want to follow two cohorts in different historic periods. You want to be sure they're in the same historic period, or pretty close.

Now, if there's no background change in the rate of

disease, that doesn't matter.

THE COURT: Okay. All right.

MR. LEGHORN: Thank you, your Honor.
BY MR. LEGHORN:

Q. Moving on to the case-control studies, can you tell us the meaning and significance of case-control studies?
A. Yes. A case-control study is a different structure. What we do is we go out and find people who have the disease of interest. So, for example, sticking with coffee and pancreas cancer, you have to find a way to get people who have got pancreas cancer. So we typically work with the hospitals, the tumor registries, the state registrar of vital records, the surgeons and oncologists who diagnose and treat this illness. And you find a way to get together 100, 200, 300 cases of pancreas cancer.
You then need to find people who do not have pancreas cancer. And the right way to do it is to identify the population from which the cases arose. And you take a random sample of that population, the source population, so that the controls represent whatever is going on in the population from which the cases were drawn.

Q. Doctor, I have a question here. Yesterday we looked at the Mele study, and I asked Dr. Smith about an asterisk that talked about that the study was run to control for age and other variables. What is the significance of that in a
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case-control study?

A. Well, what you're talking about is dealing with confounders, okay? And there are a number of ways you can deal with confounders. The first way is to match on them the study design. So in other words, if you think age is going to be a confounder, if you -- for every older case you match to an older control and for every younger case you match to a younger control. So you can deal with confounding in the study design by matching.
You can also deal with confounding in the study analysis by doing a stratified analysis. So you break the data into the old stratum, the middle-age stratum, the younger stratum, and calculate your measures of association within the strata.

So I think what you were talking about was adjusting in the analysis for age and sex and region.

Q. And when you read in a medical article the term "matched controls," what are you referring to?
A. When you read "matching," it means that the confounding issues were dealt with in the study design, not in the analysis.
Q. And what type of result does a case-control study yield?
A. Well, let's first talk about the methods, okay? So you've assembled your hundred cases of pancreas cancer and 100 people who do not have pancreas cancer, and you then ask them, or by some other mechanism reconstruct, what they've done in the
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past. So for my coffee-drinking example, we would ask each of the cases, ask each of the controls, whether they were coffee drinkers, what age they started, how many cups a day, caffeinated, decaffeinated, whatever. And then you would tally up among the cases how many were coffee drinkers. So you can see in the left panel of my 12 cases, four of them had been coffee drinkers.
And then you calculate the exposure odds among the cases. So you can see four drank coffee, eight did not, right? These are not proportions; these are odds; anyone who has ever bet on a horse or a dog or a basketball game, those are odds, they're not proportions. It's different.

Q. And what would be the proportion here?
A. Well, it would be four out of 12. But that's not the way we calculate -- we measure the association in case-control studies.
So the exposure odds among the cases are four to eight. You do the same thing among the controls. In this instance only two of the controls were coffee drinkers, so the odds are two over ten. The measure of association, then, is the ratio of the odds in the cases to the odds in the controls. And if coffee drinking was more common among people who got pancreas cancer, you see an increased odds ratio. So in this example, you see the odds in the cases is .5; the odds in the controls is .2; the ratio of the odds, or the odds ratio, is .5 over .2

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or 2.5. It says that people who got pancreas cancer were 2.5 fold times as likely to have drank coffee as people who did not get pancreas cancer.

Q. We've also talked about -- besides odds ratio in the court, we've talked about relative risk. Can you explain to us what relative risk is and how it may be different from the odds ratio?
A. Well, relative risk is more or less an umbrella term. What we're really trying to do is calculate measures of association. And so it's standard in epidemiology to scale them in the same way. They're taken as ratios. And if the ratio is 1, it means that there's no association. It doesn't matter whether it's an odds ratio or a rate ratio or a standardized mortality ratio or a standardized incidence ratio. When it's 1, there's no association. When it's greater than 1, there's a positive association. When it's less than 1, there's a negative association.
Q. And, Doctor, we've heard over the last day or two the issue of results being the product of chance. How do epidemiologists control for an observation being a product of chance?
A. Mr. Leghorn, can I ask you to go back just for one moment? I want to point out one other important thing. On the scale, you'll note that it's actually a logarithmic scale. So the distance from .1 to 1.0 is the same as from 1 to 10. And the

reason for that is that if you think of multiplying your risk twofold, it should be the same distance as dividing your risk twofold. So a tenfold risk and a .1 fold protective factor should have the same magnitude of effect. So we think of them in that way.
Okay. Now, we could go on that -

Q. And that's supported on the logarithms, the scale -A. It's on a logarithm, or logarithm scale, which is the correct way to think of it.
Q. And, Doctor, with regard to the question with regard to how epidemiologists deal with the issue of the result being a product of chance?
A. We typically calculate either p-values or 95 percent confidence intervals.
Q. And what are the significance of each of those? What is the significance of the p-values?
A. All right. Well, the p-value is the probability that you could have obtained the data you got and the association you calculate from the data by chance alone when there's really no association at all. So the premise behind the p-value is there's no association. And you say, could I have gotten this data by chance, or what's the probability it could have occurred by chance when there's really no association? So it's just a probability; it's a number between 0 and 1.
Okay. So if the P is .01, it means there's a 1 percent

chance you could have gotten the data you got by chance alone when there was really no association. By convention, P less than .05 is regarded as statistically significant.

Q. And who's that regarded as statistically significant by?
A. Well, the -- I'd say certainly the world of medicine. I'd say the world of science routinely says that's the nominal cut point for statistical significance.
Q. And what is the p-value a product of? The Court was asking a question about can we have two people for 20 years or ten people for two? Is it a product of the -- of your population, or the size of your population? What goes into factoring p-value?
A. That's a complicated thing to answer. Okay. It has to do with actually knowing the underlying distribution of the data. So if you have normally distributed data, it has to do with knowing that distribution, right? We all know what SAT scores look like where you've got a mean of 500 and a standard deviation of 100 points. And so if you are -- if you get a 700, you're two standard deviations above the mean.
So the p-value has to do with calculating the probability that you could have been that far out on the distribution by chance alone when you're really no different than the mean.

Q. And in the case of the p-value, less than .05 means that you're beyond a certain number of standard deviations?
A. Well, .05 corresponds to 1.96 standard deviations, or

roughly two deviations -- that's correct -- and that's for normal distribution.
Now, to try to answer your question, yes, the p-value has to do with the number of data points in your data set, it has to do with the size of the standard error, and it has to do with how far you are from the mean.

Q. When you say "how far you are from the mean," that's the point estimate, correct, that you're referring to?
A. Right. In other words, your measure of association is your point estimate, and in this instance we're looking at how far it is from the point estimate of 1.0; in other words, no association. So you've got a twofold relative risk with a null hypothesis of 1. The question is, is 2 meaningfully different from 1? How many standard deviations is it away? What's the probability you could have gotten that answer by chance alone when there's really no association?
Q. Now, we've also talked about confidence intervals. Can you explain what those are?
A. Yeah. A confidence interval is based on a different assumption. It's based on the assumption that the data estimates the true association. So in other words, the data you got is an estimate of the truth and that your estimate of the truth varies each time you take a sample of data from the population. So the data varies by chance, and the estimate of the association varies by chance around the truth.
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The 95 percent confidence interval is the range within which the association would fall 95 percent of the time if you did the same study over and over and over again. So you get data that says, "Gee, I find a twofold association." You calculate the interval within which you think the truth would be likely to lie if you did the same study over and over and over again an infinite number of times. And by convention we use 95 percent confidence intervals.

Q. And if the confidence interval includes 1, what is the effect?
A. Okay. If you would show the next slide, I'll explain that. Okay.
If the confidence interval includes 1, it says the null hypothesis falls within the range where I think the truth lies with 95 percent confidence; in other words, my answer is not different than the null hypothesis to a reasonable probability.

If you'd click so the confidence interval comes in.

Okay. So in my example here, if we calculated a relative risk of 2.0 and a 95 percent confidence interval that went from .9 to 4.4, what this means is we measured a twofold association; we're confident if we did the same study over and over the relative risk would fall somewhere between .9 and 4.4 95 percent of the time. Values inside the interval are regarded as compatible with the data; values outside the interval are regarded as not compatible with the data.

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Now, what the normal, or bell-shaped, curve indicates is that the truth is more likely to be close to what you measured and less likely to be farther away. And the confidence interval picks nominal cutoff points where you say, "Look, if it gets beyond that, it is just too incompatible with the data for me to conclude that the truth lies within those confidence limits."
So what you want to see is that the confidence interval does not include 1; in other words, my answer is meaningfully different from the null hypothesis, or it is very unlikely that the null hypothesis is true given the data I obtained.

Q. Now, you've heard over the last several days -- you've been sitting here -- some comments about Sir Bradford Hill's views on the meaning or the necessity for statistical significance, have you not?
A. Yes.
Q. And you have some opinions on that too; is that correct?
A. Yeah, I do. These are two quotes out of Hill's paper that we've been looking at earlier today. And one of them was put up earlier. And I think Hill was absolutely right. "Tests of significance remind us of the effects that the play of chance can create, and they instruct us in the likely magnitude of the effects." That's all they do. It's just arithmetic that allows us to assess, okay, is this reasonably consistent with chance or not? Okay.
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He goes on to say, "There are innumerable situations in which they" -- meaning tests of significance -- "are totally unnecessary, because the difference is grotesquely obvious, because it's negligible, or because, whether it's formally significant or not, it is too small to be of any practical importance."
I agree with that completely. So the point is not to get hung up on tests of significance. The point is to use them to help you interpret, "You know, could this be a chance finding or is this really something where we don't have to worry about chance? It's real. It's either too big or, conversely, it's so small that I don't care whether it's statistically significant, it's of negligible importance." That's what I think he's really saying.
Now, there's nothing in these comments that suggests that we should not look at the role of chance in Dr. Smith's calculations. There's nothing in these comments that says that p-values and confidence intervals don't matter. In fact, I would say it is exactly in instances such as this where p-values and confidence intervals do matter because we're trying to assess whether Dr. Smith's calculations are simply chance findings or whether they're compatible with something that is meaningful.

Q. Do you have an opinion whether the methodology used by Dr. Smith in evaluating the available data that benzene can cause
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APL is consistent with epidemiological matters?

A. I do. I don't think that his methods and his considerations of the literature are consistent with the practice of epidemiology or, in fact, reliable scientific methods. And I think that what he has done will cumulatively -- or cumulatively does lead to erroneous conclusions.
Q. Do you have an opinion as to whether or not incidence of APL -- or that APL is such a rare disease -- that it's not amenable to epidemiological study?
A. Well, it is amenable to epidemiologic study, and it's been studied. So this slide from Dr. Smith that basically says that it's impossible I believe is simply wrong.
Q. And, Doctor, you've reviewed, have you not, the studies relied -- and the data relied upon by Dr. Smith -A.
Yes.
Q. -- in forming his opinion?
A. Yes.
Q. And one of them we've been referring to either as the Chinese study or the Acta study; is that correct?
A. Yeah, the study that I've put in this slide. It's call it the Acta study. It's from the Academiae Medicinae Sinicae. So it's called the Chinese study.
Q. And you have reviewed this, correct?
A. Yes.
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Q. And what is your opinion with regard to the findings of this study?
A. I'm sorry. With regard to what?
Q. The findings of this study.
A. Okay. Well, let's look at the presentation of the data. In Table 1 we see the various types of ANLL, and we see that the study included 171 cases of M3, which is, of course, APL. So it's a big study. If we look at Table 2, these are the crude odds ratios; in other words, they're not adjusted for any other factor in the model. We see that there's a crude association between benzene and M3 of 1.42. And we know that since it does not have an asterisk, it is not statistically significant.
Before we leave this page, I want to look also at the number of cases of M2a, which is one of the other subtypes of acute myelogenous leukemia. There were 193. So it's slightly larger but not appreciably a different number of cases, okay?

If you would go to the next slide.

All right. This is Table 3. This is a multivariant model in which they have looked at the association between M3 and benzene, and all other factors in the model, adjusting for other factors in the model and not including in the model factors that had no significant association.

You're going too fast. Can you go back? Yeah. Take that out.

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So what you see with respect to benzene and M3 is that there is no significant association after adjusting for other factors in the model. For M2a -Now you can go to the next one. Okay.
-- the study found a 1.54 fold association and found that it was statistically significant.
Now, the important point here is whether the study had adequate power to find associations as weak as one and a half,

1.5 fold, to be statistically significant. The claim that it didn't have adequate power to look at M3 in benzene has no foundation at all.
Q. Now, Doctor, is the term "power" a term of art within epidemiology?
A. Yes, it is.
Q. And can you explain that?
A. Yeah. "Power" refers to the probability that you could detect as statistically significant some hypothesized or some aprioric association. So typically what we would say is the study had 80 percent power to detect a twofold association and to determine that it was statistically significant; in other words, you'd get the answer right 80 percent of the time because you had 80 percent power.
Q. And is there a standard within epidemiology as to what power is appropriate for a study?
A. It's a continuum, but it is largely held that -- if you've
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got 80 percent power, that's pretty good; in other words, your odds of getting it right are four out of five. That's enough.

Q. And is the power of a study a calculation?
A. Yes, it's just a calculation.
Q. And, Doctor, do you have an opinion as to whether the Chinese study, as we're calling it, had sufficient power with regard to finding a statistically significant association with APL?
A. Well, the answer is yes. And the best evidence of that is the results for M2a, in which the study had adequate power to find a 1.54 fold association to be statistically significant based on roughly the same number of cases. The power would have been a little bit lower for M3, but not a whole lot.
THE COURT: May I ask here? Power is a function of what?

THE WITNESS: Okay. Five things: First off, you have to specify your alpha error; in other words, the p-value, so .05; it has to do with the number of subjects in the study, you know, let's talk about cohort studies, since that's the way we've been doing it, then we'll talk about case-control studies. So it's the number of persons in the study; the number of person years of observation; the allocation of subjects between exposed and non-exposed, or you could alternatively say the number in the exposed group, the number in the non-exposed group, or you could alternatively say the

proportion exposed. And one other factor. What is it? Oh, and the relative risk you hypothesize.

Okay. For a case-control study, it's again the number of subjects, the allocation ratio between cases and controls. This time it's the prevalence of exposure; the relative risk; and, of course, the alpha error or the p-value.
BY MR. LEGHORN:

Q. Doctor, one of the things that you just mentioned was the number of cases. Do you recall in the Chinese study how many controls were matched to cases?
A. I'm not sure they matched, but they used two times as many controls for each case. So the allocation ratio was 1:2.
Q. And that's a ratio that would be factored into the power calculation?
A. Yes. In fact, one of the ways you can increase your power in a case-control study is to use more controls, and the decision as to whether you use more cases or more controls has to do with which one you have access to and how much money it costs to include them. So that's purely a logistical issue as to which way -- how you choose your allocation. It doesn't change the results.
MR. LEGHORN: Your Honor, before going on to another study, do you have any further -THE
COURT: I'm satisfied.
BY MR. LEGHORN:

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Q. Yesterday the Pliofilm cohort was mentioned by Dr. Smith. Can you tell us what the Pliofilm cohort or group of studies are?
A. Yes. The Pliofilm cohort refers to a cohort of workers at the BF Goodrich facility who were making Pliofilm rubber. And as I recall, what they were doing was dissolving latex rubber in benzene and then letting the slurry spread out and let the benzene evaporate out of it, so that they could make very thin rubber membranes which were called Pliofilm.
Okay. It's a very important cohort for two reasons: The first is that it's a pure benzene exposure. There were no other chemicals in use. It wasn't looking at gasoline, diesel fuel, paint solvents, it was benzene. Okay. And when I say "pure benzene," I mean it was probably industrial grade or technical grade, but it was meant to be pure benzene.

The second reason it's important is that BF Goodrich did very good industrial hygiene monitoring. They measured the exposures, so there were historic records of exposure to benzene. And so it allowed the occupational health community, and now the cancer epidemiology community, to look very carefully at the relationship between disease risk and measured exposures to benzene over time. So it is probably one of the most important -- or the most important data sets in looking at the evidence of carcinogenicity of benzene to humans.

Q. Doctor, I noticed on the bottom of the slide, which is one 86d28023-5cad-4297-9232-e09c00039d07

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of Dr. Smith's slides, the date of 1981; is that correct?

A. Yes.
Q. Is this a cohort that, as we discussed earlier, may have been followed forward in time?
A. Yes. In fact, the first report from this cohort came out in 1977. And at that point it was a retrospective study; in other words, the investigators at NIOSH were looking back over time at who had worked in the plant, over what years they'd worked, what jobs they'd held and what their exposure levels were. The cohort has continued to be followed forward since that 1977 report, and has been updated periodically since then.
Q. Doctor, in this slide there is also the mention of certain codes. Can you tell us what those codes mean?
A. Yeah. My boxes have now covered it up. Just take that out.
So the ICD is the International Classification of Diseases; the 7th revision was in effect when this paper was published; Codes ICD 200 to 205 included all lymphatic and hematopoetic cancers. That would be the leukemias and lymphomas. And so you can see the results for all causes of death. They saw 180 deaths observed, they expected 161. The ratio of 180 to 161 is the standardized mortality ratio, or SMR, multiplied times 100, it's 111. I always think of that as

1.11. So when you look across all causes of death, there was an 11 percent excess in this population.
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When you restrict your view to all leukemias and lymphomas, you see there were ten deaths observed with only

3.03 expected. So the rate ratio is 3.3 fold. And you can see they've annotated that that is statistically significant with a p-value of less than .01.
Now, there's an important point here. This paper shows increased risk of all leukemias and lymphomas; however, it's not due to excesses of each and every type of leukemia and lymphoma, it is due to an excess of acute myologic leukemia, which is ICD Code 204. You see for 204 -- actually, I'm sorry, that's all leukemias together. What you see is seven observed versus 1.25 expected.

If you take the difference between the 7 and the 1.25, there's about six extra leukemias. If you then go up to the row above that and you say, "You know, when you look at all leukemias and lymphomas together, there was an excess of seven, but six of them were leukemias, so there's no excess of lymphoma in this study, it's the excess of leukemia which is driving all of the numbers."

And for the leukemias, the ICD 204, the rate ratio is 5.6 fold, and the p-value is less than .001. This is not a chance finding, okay? That's a big risk, 5.6 fold, and there's no question it has nothing to do with chance.

Q. And this is a -- as we talked about, this is a cohort that has been followed, correct?
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A. That's correct.
Q. And there are various studies that have followed this, correct?
A. Yes.
Q. I'm showing you what is a study by Mary Paxton; is that right?
A. Right. Mary Paxton updated the analysis of the cohort and published it in risk analysis in 1994. One of the things she did that's very valuable is she showed the diagnoses of all the cases of lymphohematopoietic cancer, lymphomas and leukemias. And here it is: Her Table 4, you can see the yellow box, I've highlighted the cause of death. And here are the ICD codes. And 205.0 is AML.
Put that box in, if you would.

Okay. The upper half of that table shows the original cases from the Rinsky study, and then the lower half shows the cases added in the update.

All right. When Rinsky published his paper, there was only one case that was coded to AML 205.0, and it was recorded as an acute myeloblastic leukemia; that's a specific subtype of AML. There was no case of APL recorded in that study. In a 1994 update there were two additional cases coded to 205.0. They were both written as acute myeloid leukemia. You can see there are two of them. The second from the bottom is the second AML, or acute myeloid leukemia. Neither of these was

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diagnosed or recorded as an APL.

Now, Dr. Smith claims that those could be APLs but he doesn't know. And what is true is that the ICD code of 205.0 would include APL. I think I misspoke. He said -- earlier I said "AML" where I meant "APL."

Okay. So 205.0 includes APL. My point is that in not any instance was there a cause of death written in as "acute promyelocytic leukemia."

Q. Where, Doctor, would you generally find the cause of death?
A. Well, often from the death certificate, but sometimes studies are based on the review of medical records to determine the underlying cause of death.
Q. In the instance of death certificates, who fills those out?
A. Physicians do.
Q. Have you filled out death certificates?
A. On many occasions; yes.
Q. And, Doctor, do you have an opinion whether Rinsky supports the conclusion that -- or Rinsky -- the Pliofilm cohort supports -- the data there supports the conclusion that benzene exposure causes APL?
A. Well, it does not. There is no case of APL in that cohort.
Q. Now, did you look at some other epidemiological studies,
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Doctor?

A. Yes.
Q. And was one of them the Zhang study published in 2002?
A. Yes; I looked at that.
Q. And in looking at that, is that a study that looked at FAB subtypes?
A. Well, the Zhang study collates the results from a number of studies published in the 1980s and 1990s that looked at FAB subtypes and their cytogenics, their carrier types. So it shows the Mitelman in '81, Golomb in '82, the Groupe study in '84, et cetera.
Q. Did you make any observations when looking at the Zhang study?
A. I'm not sure what you're asking.
Q. Well, Dr. Smith was a co-author of this, correct?
A. Yes.
Q. And some of this data was used by Dr. Smith in performing his calculations for the purposes of this hearing, correct?
A. Yes.
Q. Did you make any observations about the treatment of the data in this study co-authored by Dr. Zhang, Eastmond, and I believe -- I believe Eastmond and Smith?
A. Yes. What I heard him say yesterday is that some of the diagnoses of M3 in this study were wrong. So what he published with Zhang shows that these were M3s, and yesterday he said
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some of them were not M3s.

Q.
Any other observations?
A. Yes. Two of the cases in the Golomb study, which he published with Zhang, had exposures where if you look at his heading, it says, "Abnormal Carrier Type of Selected Leukemia Patients with Likely Prior Exposure to Benzene." Yesterday I heard him say that these two that are highlighted with the arrows, one exposed to paint and one in the leather industry, he felt were not likely exposed to benzene.
Q.
Doctor, have you reviewed the Golomb study?
A.
Yes.
Q. And can you tell us what the Golomb study was investigating?
A.
Yes. This is a case-control study in which -If you could show the next arrow.
-- they're looking at past exposures to insecticides, chemicals and solvents or petroleum products. There were no measurements of benzene; this is not a study of benzene exposure. It's a study of chemical exposures and a pretty broad set of families of chemicals.

Q. And, Doctor, this would be, in our dichotomy of types of studies, a case-control study?
A.
This is a case-control study.
Q. And can you tell us what you did in your analysis of Dr. Smith's analysis of the Golomb data?
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A. Yeah. I went back carefully over the methods by which he reached his conclusions and tried to reconstruct what he had done. And so the first thing is that he points out that one of eight, or twelve and a half percent, of workers exposed to petroleum products had APL, and he says these were the workers who had likely benzene exposure. So he includes these as gas station attendants, steel crane operators, truck drivers and mechanics. And we see that one of these is an M3, the one that's highlighted. So there's one M3 among eight workers who he says likely had benzene exposure.
Q. And these are the cases of leukemia that we would be looking at in a case-control study?
A. Well, what Golomb has actually done is he's -- the whole study concerns cases of leukemia, but he's separated them out by type. And so he's comparing the M3s to the other ANLLs.
Q. And, Doctor, we're talking about -- the Golomb study was 1982, correct?
A. Well, this is from Dr. Smith's PowerPoint. Let me get the actual study out. I don't recall. Yes, it was published in August 1982.
Q. And how would you make this -- these particular slides, going over to this eight cases of leukemia, where did you get the slide from?
A. This was from Dr. Smith's PowerPoint that you sent to me over the weekend.
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Q. And how many were in Golomb's cases group as opposed to the control group? How many subjects, in exposed patients?
A. Yeah, let's do it by exposure because that's how Golomb presents it. There were 16 patients in Golomb's paper that he felt were exposed, and they're listed here in his -- in Golomb's Table 3.
Q. Was he looking at exposure or occupation?
A. Well, he was looking -- they had asked people about their past occupations and had grouped them by the inferred exposures that they had in their past occupations, and hobbies, in fact. They also asked about hobbies.
Q. But he does not break out a separate category for benzene exposure, correct?
A. No, he does not.
Q. And he doesn't document any benzene exposure; is that correct?
A. That is correct.
Q. And out of this group of 16, Dr. Smith used just the eight in petroleum products, correct?
A. That's correct. Dr. Smith restricted his purview to the eight at the bottom half of this Golomb Table 3.
Q. And is this the same eight that he referred to as exposed benzene in the Zhang paper?
A. No. No. The Zhang paper clearly included the paint factory worker, which you see as Case No. 63, and the leather

worker as Case 62.

Q. So -A.
So in Zhang, Dr. Smith felt that these people who had these other exposures in the upper half of the table, some of them were clearly exposed to benzene. And so the question is, how come he could throw them out now?
Q. The question is, Doctor, in reviewing Dr. Smith's declaration, supplemental declaration, and listening to his testimony, did he offer any explanation as to why these two, the leather worker and the paint worker, were no longer included?
A. I don't recall any such explanation.
Q. Now, Dr. Smith made some calculations, correct?
A. Yes.
Q. And some of that was -- and this is a slide outlining his calculations, correct?
A. Yes.
Q. And he indicates that there were three APL cases in the unexposed patients, correct?
A. Yes.
Q. And did you make any investigation as to whether that was correct?
A. Yeah. I went back through Golomb's tables and counted up the M3s. This is Golomb's Table 1. It shows there were four M3s. Now, these are the people who were non-exposed and who

did not have hobby exposure. So there were four.
And then if you go to the next slide -

Q. Before we go to the next slide, Doctor, you heard Dr. Smith yesterday say that if you had -- if you were diagnosed as an M3 and had an abnormality at Chromosome 17, that was an appropriate inclusion in -- an appropriate diagnosis of M3, correct?
A. I believe that's what he said.
Q. And looking at the four cases that you've highlighted here of M3, can you tell us whether or not those all have an abnormality at Chromosome 17?
A. Yes, they did. Case 35 is a t(15;17), Case 38 is a 17p+Q-, Case 41 is a t(15;17), and Case 42 is a t(15;17).
Q. Now, you were going to say something about the unexposed with hobbies?
A. Right. Now, this is Golomb's Table 2. This tabulates the patients who did not have occupational exposure but who were felt to have hobby exposure. And you can see there is a fifth case of M3. This one had no abnormality of Chromosome 17.
Q. And you heard Dr. Smith say this is the one he excluded, correct?
A. I believe that's what he said.
Q. And in reviewing the materials provided in his reports before the hearing and his deposition and at the trial, you reviewed his deposition, correct?
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A. I did.
Q. Was there any explanation as to why one of the exposed with a Chromosome 17 abnormality was not included?
A. I don't think so.
Q. Now, again, this is Dr. Smith's slide. Did you go on and review further what he did here?
A. Yes. So now he makes his calculation. So what he says is the incidence of APL is two times higher in patients with probable exposure to benzene than in unexposed patients. So he's comparing the 12.5 percent proportion to either 5.2 or 6.9 percent that he calculates after excluding eight people whose exposures that he didn't like anymore, or didn't consider, to the three or four cases among the 58 people who were not exposed after excluding one or two of the cases that he didn't like from that group.
Q. Did you go ahead and recalculate the data with certain assumptions using -A.
Yeah. I've recalculated it four different ways.
Q. Okay. Can we go through them?
A. Yeah. Okay. So this is a fairly standard representation of how you calculate an odds ratio from case-control data. You can see it's presented in a 2-by-2 table. The first row is the M3 cases: There was one case among those exposed to petroleum products and three among those not exposed. So what I'm doing here is I'm doing it Dr. Smith's way by excluding -86d28023-5cad-4297-9232-e09c00039d07

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Q. The two that he said were -A.
Yeah, the two that he said should be excluded, and I've also restricted the analysis to only eight of the 16 exposed subjects.
So in the left-hand column where you can see "exposed to petroleum products," I've only allowed eight of them in. When you make that calculation, you get an odds ratio of 2.62, you get a p-value of .42, and the confidence interval is extremely wide, going from .24 to 28.75. And so what this is saying is even though there's a 2.6 fold association, it's entirely compatible with a chance finding.

Now, this is where I think Hill would say you don't need a p-value because you don't have any data. When you're trying to make a calculation based on one in three, you've got such small numbers, the p-value is not terribly important. This is chance.

Q. And -A.
Okay.
Q. -- did you do, then, the calculation assuming in the exposed -- the non-exposed group that all four with abnormalities at Chromosome 17 were included?
A. Yup. If you would click.
Okay. So now I put one of the APLs back in -- so now we have four in one -- the one among the exposed and four among the non-exposed. And I just realized there's a minor error in

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my right-hand column that totals to 59; it should total to 58. So I should have taken one out of the 55. So it will change the number in a very small way. I apologize for that.
Okay. So if we include four cases, four M3s among the non-exposed and one among the exposed, now we get an odds ratio of 1.96 and a p-value of .57. Again, no statistically significant association; this is completely compatible with chance.

Q. And looking at -- you went on and did a couple of other calculations with the Golomb table?
A. I did it again this time using all five cases that were reported in the paper. Now we see the odds ratio -- and still restricting to the eight that Dr. Smith said yesterday were the exposed. Now the odds ratio is 1.51, the p-value is .72, and again is -- so this is just chance, okay?
Then I did it again, this time using all the data in the Golomb paper. So using all 16 people who were exposed to petroleum products -- or I should say exposed from Golomb's Table 2, and all five cases. When you do this calculation, you get an odds ratio of .71 and a p-value of .76. So there's no association at all.

Q. Doctor, to summarize your evaluation of the Golomb data, did you come to some overall conclusions?
A. Yes. All right. He makes a number of errors that make his conclusions unreliable. First, he discards two APL cases
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from the non-exposed group for what I regard as arbitrary reasons.

Q. Why do you describe those as arbitrary?
A. Because there's no scientific -- there's no valid reason to exclude them.
Q. What do you -A.
You could argue about the one that didn't have any cytogenetic abnormality of Chromosome 16, but I don't think you can exclude any of the ones that do have a 17 abnormality.
Q. And earlier in your answer you referred to Chromosome 16. Did you mean 17?
A. I didn't even know I said "16." I should not have said "16." I apologize.
Q. Okay. Going on, any other observations?
A. Okay. Second point: He discards eight subjects from the exposed group for arbitrary reasons leading to an overestimate of the proportion of APL among the exposed subjects.
Third, he didn't calculate odds ratios. What he calculated is a ratio of proportions. Back when I went through cases he cites, he talked about odds ratios. He did not do the calculations right.

Fourth, he makes no calculation of p-values to confidence intervals; in fact, his results, no matter who you exclude or include, are entirely compatible with chance. Any fair and evenhanded treatment of the Golomb data shows there is no

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association whatsoever between the exposures in that paper and APL.
And then lastly, the Golomb paper is not a test of whether benzene exposure is associated with APL. It contains no knowledge whatsoever regarding benzene exposure.
MR. LEGHORN: Your Honor?
THE COURT: Perfect place to pause.
MR. LEGHORN: I was going to say we're going on to another study, so...
THE COURT: All right. We'll resume on the regular schedule, nine o'clock in the morning.
MR. LEGHORN: Thank you, your Honor.
THE WITNESS: Thank you, your Honor.
THE CLERK: All rise. Court is in recess.
(The proceedings adjourned at 1:01 p.m.)
C E R T I F I C A T E
I, Marcia G. Patrisso, RMR, CRR, Official Reporter of the United States District Court, do hereby certify that the foregoing transcript constitutes, to the best of my skill and ability, a true and accurate transcription of my stenotype notes taken in the matter of Civil Action No. 07-11944-GAO, Brian K. Milward, et al, v. Acuity Specialty Products Group, Inc., et al.
/s/ Marcia G. PatrissoMARCIA G. PATRISSO, RMR, CRROfficial Court Reporter

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