14TH JUDICIAL DISTRICT COURT

PARISH OF CALCASIEU

STATE OF LOUISIANA

STEVE LEBLANC, ET AL NO. 91-1145

VS.

CONOCO, INC., ET AL

Deposition of RICHARD D. IRONS, Ph.D., taken in the above-entitled cause, pursuant to the following stipulation, before Julie L. Samford, Certified Shorthand Reporter, at the law offices of Phelps Dunbar, 400 Poydras Street, New Orleans, Louisiana, at 9:00 a.m. on the 27th day of October, 1992.

APPEARANCES:

Representing the Plaintiffs:

HOBSON & FERGUSON
BY: THEODORE M. FLERLAGE
2190 Harrison Avenue
Beaumont, Texas 77701

Representing Defendant Moore & Companies:

PHELPS DUNBAR
BY: BARBARA L. ARRAS
Texaco Center
400 Poydras Street
New Orleans, Louisiana 70130-3245

Representing Defendant Conoco, Inc., and Canadian Oxy Offshore Production Company:

JONES, TETE, NOLEN, HANCHEY, SWIFT & SPEARS
BY: KENNETH R. SPEARS
First Federal Building
1135 Lakeshore Drive
P.O. Box 910
Lake Charles, Louisiana 70602

Representing Insurance Company of North America:

GUILLORY & McCALL
BY: WILLIAM T. McCALL
901 Lakeshore Drive, Suite 836
Lake Charles, Louisiana 70601

Representing PPG:

STOCKWELL, SIEVERT, VICELLIO, CLEMENTS & SHADDOCK
BY: BENJAMIN J. GUILBEAU, JR.
One Lakeside Plaza
Lake Charles, Louisiana 70601

APPEARANCES: (Continued)

Representing Oxy USA, Inc.:

E.W. HACK
OXY, USA, INC.
SENIOR COUNSEL, LEGAL DIVISION
110 West 7th Street
Tulsa, Oklahoma 74119

Representing Conoco, Inc.:

SUSAN FROEHLY TEICH
CONOCO, INC.
COUNSEL, LEGAL DEPARTMENT
600 North Dairy Ashford
Houston, Texas 77079

S T I P U L A T I O N

It is stipulated and agreed by and among counsel for the parties hereto that the deposition of the aforementioned witness is hereby being taken pursuant to the Louisiana Code of Civil Procedure for all purposes, in accordance with law;

That all objections except as to the form of the question and responsiveness of the answer are hereby reserved until such time as this deposition, or any part thereof, may be used or sought to be used in evidence.

E X H I B I T S

RICHARD D. IRONS, Ph.D., 4200 East 9th Avenue, Denver, Colorado, after being first duly sworn in the cause, testified as follows:

EXAMINATION

BY MR. FLERLAGE:

Q. Doctor, for the record my name is Ted Flerlage. I am representing the two plaintiffs who are left in this case. Are you here for a deposition in the Stelly and LeBlanc cases?

A. Yes.

Q. And have you prepared any materials which would be a report or a summary of what your findings are?

A. In writing, no.

Q. Do I take that to mean that you have an oral report of some type that you have given to somebody?

A. I have an opinion, yes.

Q. Has that been given to anyone in this room?

A. Yes.

Q. Who is that?

A. Ms. Arras.

Q. Was that done by telephone, or this

morning, or how did you do it?

A. By telephone and in meeting.

Q. Okay. Can you tell me briefly what you told her at either one of those two places?

MR. McCALL: Excuse me. I am going to object, Ted. Again, I think you are getting into an area of attorney work product about what was discussed between counsel and a witness, and I object to that. You can ask who was there, when and what, and I don't have a problem with that, but the actual details of the conversation I think are privileged.

MR. FLERLAGE: I'm not asking for a conversation, Counsel. I am just asking for his opinion as expressed to Ms. Arras at either one of the two occasions, and if I limit it to that, I think I am entitled to get that information. That's not what I would think would be either work product or attorney-client privilege.

MR. McCALL: Just his opinions he has expressed?

MR. FLERLAGE: That's all I am asking.

A. There is insufficient evidence to suggest that multiple myeloma is associated with exposure to benzene, butadiene or ethylene oxide.

Q. Have you gotten into the issue with regard to vinyl chloride?

A. No, I have not.

Q. Are you going to express any opinion with regard to vinyl chloride?

A. If I am asked to do so, I will, but at the present time I haven't formulated an opinion.

Q. Okay. Now you put it in terms of insufficient evidence. What do you mean by "evidence"?

A. Data in the scientific and medical literature that would support a causal relationship.

Q. Are you limiting that to epidemiological literature, or does it extend beyond epidemiological literature into some other scientific spectrum?

A. Epidemiology certainly plays a major role in that process. If you have human data, especially that's reliable, you should use it.

By the same token, experimental animal

data and mechanistic data is extremely important to aid in interpreting issues that are raised through epidemiology studies.

Q. In support of your opinion that you have just expressed, are you relying on any human data in particular?

A. Yes, the epidemiology literature that I brought with me today.

Q. All right. And that's in the black notebook that I have been pawing through here? I will get to that in a minute then. With regard to any other materials -- I think the first set here is epidemiology; would that be correct?

A. The first set is epidemiology, related specifically to the issue of multiple myeloma.

Q. And the second category?

A. The second category includes basically some of my own work, including a book chapter in a clinical toxicology text by the title of "Hazardous Materials Toxicology," and I brought that because that summarizes quite adequately my opinions with respect to the evidence for ethylene oxide and for butadiene.

I have brought one of my latest papers, which speaks to the issue of the target cell in

certainly benzene bone marrow toxicity. I brought just a couple of papers that deal with the issue of the ontogeny of multiple myeloma and its origin.

Q. And that would be the next category?

A. Yes.

Q. And I have brought, by no means not all, but I brought some of the papers, including my own, which support my opinions with respect to butadiene and ethylene oxide.

Q. And that's in the final category that you have got in the loose-leaf binder?

A. Yes.

Q. Okay. Have you been asked to look into any cause and effect relationship of vinyl chloride and multiple myeloma?

A. No.

Q. Okay. So at this point, anyway, you don't intend to go any further and look into that?

A. Not unless I am asked to do so.

(EXHIBIT NO. 1 WAS MARKED)

BY MR. FLERLAGE:

Q. Okay. All right, Doctor. It's a little bit late for this, but anyway I've got Irons Exhibit No. 1 as the notice of deposition. Have you seen that?

A. Yes.

Q. In addition to the materials you have just described in your notebook, what other materials did you bring which would be responsive to the notice of deposition?

A. I brought the materials I have received from Ms. Arras, including a letter that accompanied medical records that I received and some summaries that I received from her. I am missing one letter that I have misplaced.

Q. That's probably a smoking gun, I guess, right?

A. I know what the substance was. It notified me that Fautheree was being eliminated from the suit.

Q. So with the exception of that letter then, this would be the correspondence that you received?

A. Yes, plus the medical records, which I have not brought with me.

Q. Now the medical records you received would be the eight-inch thing that we described yesterday?

A. Yes.

Q. And you have got a summary also of

that?

A. That's in there.

Q. Have you summarized the records independent of counsel?

A. Yes, to a very minimal extent, just so that I keep track of time and place.

Q. So you have got two sheets of handwritten notes here, which would be one on LeBlanc and one on Stelly?

A. Yes.

Q. And this is in your handwriting?

A. Yes.

Q. The LeBlanc, and Stelly is also?

A. Yes.

Q. Is this a current copy of your CV?

A. Yes.

Q. And that would be up-to-date as far as publication is concerned?

A. To the day.

Q. Okay.

A. I can't do better than that.

Q. No.

(EXHIBIT NO. 2 WAS MARKED)

BY MR. FLERLAGE:

Q. I have had that marked for the record

as Exhibit No. 2, and that will be the CV.

Exhibit No. 3 I will mark as the folder that the materials that we have just gone through came in, and then we can go through this and mark them with letters and suffixes if it's okay.

3-A and 3-B would be the pages of handwritten notes from the doctor, one on LeBlanc and one on Stelly.

The next items will be as described by the doctor, the medical records summary and the work history of Maurice Stelly, Jr., which will be C and D, and the medical records summary and the work history summary of Steve LeBlanc, E and F.

(EXHIBIT NOS. 3-A THROUGH 3-F WERE MARKED)

MR. McCALL: Which one goes first, Ted?

The medical summary first?

MR. FLERLAGE: The medical summary first, yeah.

BY MR. FLERLAGE:

Q. And then you have some deposition summaries in here, I take it, which were supplied by counsel.

A. Yes.

Q. And the summaries are Volumes I and II of the LeBlanc deposition?

A. Yes.
Q. And then the Stelly deposition?
A. Yes.
Q. Okay. Have you received any other deposition summaries or depositions in this case?
A. I have seen Volumes I and II of the LeBlanc deposition. I have seen the Stelly deposition. I have no other summaries that I am aware of.
Q. Have you reviewed any other depositions with regard to this case, whether from a fact witness or an expert witness?
A. No.
MR. FLERLAGE: Okay. Why don't we just mark these G, H, and I.
(EXHIBIT NOS. 3-G, 3-H, AND 3-I WERE MARKED)
BY MR. FLERLAGE:
Q. Except for the one piece of correspondence that I haven't had numbered, is that the sum and substance of your file in the case?
A. Yes, with respect to what I have received.
Q. Yes. Thank you. And have you done any other research or acquired any other materials with regard to this case?

A. Well, in response to the deposition notice, I brought with me all other materials that I have written that deal with the case. This is just some notes I took on my first phone call with Ms. Arras.

Q. And at the top is written "Radiation, Farming-Livestock" and ""Coal Tar-Asphalt."

A. Yes.

Q. Would they be potential exposures involved in the case?

A. When she mentioned multiple myeloma, those were my first thoughts with respect to occupations or exposures, that there is literature to suggest a causal relationship.

Q. Okay. And this was initially, without doing any specific research in the case or knowing anything about specific exposures; is that right?

A. That's right.

Q. So this would be very early on in the case when you first contacted Ms. Arras?

A. When she contacted me, yes.

(EXHIBIT NO. 3-J WAS MARKED)

Q. Doctor, I have been referring to the Richard Irons deposition which was dated or done December 17th, 1991, just as a framework for

background information and what have you, and that was in the case of Ellis versus a number of defendants. Do you remember taking that deposition or giving that deposition?

A. Yes.

Q. That was December. Since that time, without going into the CV, have your qualifications or educational background or any of those things changed in any degree?

A. No.

Q. With regard to what you are doing on a day-to-day basis with your occupation, has that changed in any sense since December?

A. No.

Q. Do you have the same grants and the same contracts that you described at that time that you are still working on, on an ongoing basis?

A. Yes. The same ones that I have, I had then; vice versa, the same ones I had pending then, I have pending now.

Q. Have you sought any other grants from either the government or any other independent agency for research?

A. Yes.

Q. What areas would they be in?

A. Biomonitoring for cancer, the National Cancer Institute, would be the one that I currently have in preparation right now, and I expect over the course of the next year I will probably propose and submit one or two additional grants.

Q. Would they be in areas which are germane to the issues of this case?

A. Yes.

Q. And in what way?

A. Virtually all my research is focused on mechanisms of bone marrow toxicity and leukemogenesis, either in animals or man, and understanding those mechanisms, so anything that I am likely to submit as a research proposal is going to have some bearing on it.

Q. To whom have you submitted the proposals?

A. I am in the process of tendering a submission to the National Cancer Institute. I have not yet submitted it, but will by the middle of next month.

Q. Have you submitted any further proposals than those described in the December deposition to either the API or CMA?

A. I don't believe so.

Q. All right. Do you still have ongoing research on behalf of API and CMA?
A. Yes.
Q. Same projects you discussed then?
A. Yes.
Q. Have you addressed any meetings of membership of the API or CMA since that time?
A. Memberships meetings? I attended a workshop that involved EPA, API, representatives of various regulatory agencies in Warrenton, Virginia, last month.
Q. What was the substance of that meeting?
A. State of the art of the science as it forms a biological basis for evaluating risk assessment.
Q. That would be the present state of the art?
A. Yes.
Q. Who else gave a presentation or spoke at that meeting?
A. Bernie Goldstein from Rutgers, several people from the Environmental Protection Agency, Canadian Environmental -- it's not the Environmental Protection Agency, but Canadian Health and Welfare, Canada, Robert Snyder from

Rutgers, Michelle Midensky from C.I.I.T., Raymond Tyce from Research Triangle Park, a variety of different researchers and regulators who were interested in benzene toxicity.

Q. Was there a report generated or a publication generated from that meeting?

A. No. It was a very informal discussion.

Q. Was there a consensus reached among the people who gave presentations, to the best of your knowledge?

A. In a way, yes, and that is that the only answer that is going to improve the process of risk assessment for benzene is going to be mechanistic biologic studies that provide a clear understanding of the mechanism in action.

Q. Which would be the pathogenesis essentially of how the metabolites affect the cell structure?

A. That would be a fair description.

Q. Would that also be true of the other chemicals we are talking about, butadiene and/or ethylene oxide?

A. You are asking someone who --

Q. I'm sorry. Let me strike that. You didn't discuss any of the other chemicals at this

particular meeting?

A. No.

Q. Let me get to that later then. Was this the only presentation or meeting of any type that you had with organizations such as this, CMA, API?

A. I probably have given a progress report to -- yes, I gave a progress report to CMA on my butadiene research at roughly the same time.

Q. So you have a reasonably new butadiene paper here?

A. I have a butadiene paper in submission. It's not yet in press, so it's not in this folder.

Q. What is the gist of that paper?

A. It characterizes the cytocon specificity of the cell populations that are sensitive to the monoepoxy epoxibutene, which is the monoepoxy metabolite of butadiene.

Q. Is there an English translation for what you just said?

A. We are looking at the alterations that the metabolites of butadiene cause on bone marrow cells in culture.

Q. Would that be similar to the research that has already been done for benzene, for

instance?

A. Yes.

Q. You have already gone that route with benzene, I take it, and you have opinions with regard to how benzene affects -- the metabolites of benzene, at least, affect the marrow; is that correct?

A. Yes.

Q. So you are doing the same type of studies with regard to butadiene?

A. Yes.

Q. Do you have any conclusions with regard to the effects of butadiene? And again, I am limiting that to the bone marrow.

A. To the extent that we have examined it, which is the mouse, I think that it's fair to say that butadiene does not behave in a manner that's similar to benzene.

Q. Okay. In what ways would it be different or characterized as different?

A. It does different things to different cells. That pretty well summarizes it.

Q. Different stem cells, or different types of groups of cells or classifications of cells?

A. Well, it depends how you define "stem cell." Different cells that are at different stages of differentiation.

Q. Would it be fair to say then that, at least in your opinion, with regard to the present status of your research into butadiene, that it does not do the same things to the same cells that the benzene would do?

A. Yes.

Q. Okay. That is sort of a summation of the whole?

A. Yes, in the mouse.

Q. In the mouse? Can you translate those experiments into the human experience?

A. We are beginning to do that now. We are actively involved in directly comparing the two species, but we have no data on which to make any statements of the similarities or differences at this point.

Q. Have you been able to get marrow specimens, human marrow specimens, to use for your research?

A. Yes.

Q. You talked about some sources that you had back in December. Have those changed at all

for marrow?

A. Yes.

Q. In what way?

A. I am buying marrow now from human volunteers.

Q. So you're harvesting marrow from people in the same sense that hospitals do for --

A. Yes.

Q. Okay. Are there any specific marrow and/or blood types that you are after when you are harvesting?

A. I don't understand the question.

Q. Is there a type of human blood type or human marrow component which would be more susceptible in your opinion to any of these processes?

A. You mean a particular individual?

Q. Yes.

A. No. No, at this point we are looking at normal individuals and we are looking at normal bone marrow. We are not distinguishing or selecting marrow on any basis I can think of, except that they be AIDS-free, that women not be pregnant, and we are keeping information such as smoking history, that type of thing.

Q. When you do the harvest, do you do it from the iliac crest or do you do it from the sternum? How do you do it?

A. I don't know anybody that does sternum anymore.

Q. Okay.

A. Iliac crest.

Q. What quantity do you receive from the donors?

A. It varies, but normally 5 ML's.

Q. You have some papers, I believe, that you brought with you on ethylene oxide also.

A. Yes.

Q. And is there any ongoing research which would be similar to what you have just described in the butadiene concept for ethylene oxide?

A. Not to my knowledge; certainly not in my laboratory.

Q. What would be your opinion of the capability of ethylene oxide to cause bone marrow changes as a result of exposure to ethylene oxide?

A. The answer to that question depends on a lot of variables. If you are talking about an in vitro culture system where you introduce ethylene oxide into the culture directly, very much

like we are with metabolites, benzene or butadiene, I would surely expect to see some toxicity, because ethylene oxide is a direct-acting, very reactive molecule. In vivo, I know of no -- I have no basis on which to give you an informed answer to that.

Q. Either animal or otherwise?

A. No. It's clearly reactive. It will cause toxicity directly to cells in the blood. I think that's fairly well established, so the issue of whether or not ethylene oxide in high concentrations can be toxic I don't think is controversial; it's a question of what its potential for causing leukemia or lymphoma is, and those are totally different subjects.

Q. Would your opinion that ethylene oxide does not cause or did not in this case cause the multiple myelomas that these gentlemen purportedly have be based on the epidemiology with regard to ethylene oxide?

A. Yes.

Q. The documents that you have brought with you, I take it they are the only copies that are here at present.

A. Yes.

Q. Do you mind leaving those with the

court reporter?

A. If I can get these copied and returned to me, that would be fine.

MR. McCALL: We can do that. We can have them photocopied and ship them back to you; is that okay?

THE WITNESS: Yeah.

BY MR. FLERLAGE:

Q. Since you have described the categories, and we may be referring to the individual articles at some time during the deposition, if that happens I will have them individually marked, but for purposes of record-keeping, I will call it Exhibit 5 for the whole package.

(EXHIBIT NO. 5 WAS MARKED)

BY MR. FLERLAGE:

Q. Doctor, do you understand this to be a discovery deposition?

A. Yes.

Q. And are you scheduled to appear at the trial of the case?

A. It is my understanding that if this case goes to trial, I will testify.

Q. Do you know when the trial date is?

A. No.

Q. If I told you November 16th as a startup time or potential startup time, would you have anything in your schedule which would interfere with your testimony sometime thereafter?

A. Teaching. It's a matter of scheduling in between my lecturing and teaching responsibilities.

Q. You believe you could make sufficient time to get to Lake Charles?

A. Yes.

Q. And the testimony and then to leave, would that take approximately three days out of your schedule?

A. Two or three, depending upon how it goes, connections and that type of thing.

Q. Now you testified that you were retained in these cases by Ms. Arras?

A. Yes.

Q. And are you also, to the best of your knowledge, working on behalf of the other defendants in the case?

A. To the best of my knowledge, yes.

Q. So the testimony you give today will be on behalf of any defendants remaining?

A. I assume so. My testimony is my testimony irrespective of who's here.

Q. For purposes of litigation such as this, do you have a particular billing rate?

A. I have a standard billing rate that I use for all consulting activities, whether it's litigation, consultation to various industries or agencies, and that's 300 an hour. The only exception is when I provide an advisory role to regulatory agencies or the U.S. government, I go by whatever the standard daily rate is.

Q. Do you have any invoices for work performed to this point in these two cases?

A. No.

Q. Can you estimate how many hours you have applied to the LeBlanc and Stelly evaluations?

A. Yes. I wrote this down. I brought this in response to the deposition notice. This is a record of my hours to date.

Q. Okay. Now this is LeBlanc, et al, and it has dates over on the left hand, next to the margin, and then these are hours on this side?

A. Yes.

Q. And each of these hours would have been at the rate of $300 per hour?

A. Yes.
Q. There is no total at the bottom here. May I have this marked as Exhibit 6?
A. That, I would like back.
(EXHIBIT NO. 6 WAS MARKED)
BY MR. FLERLAGE:
Q. This comes up to 10-26, which is travel, and that would be to get here?
A. Yes.
Q. And then 10-25 would be copying articles and record review?
A. Yes.
Q. That would be these articles?
A. Yes.
Q. For courtroom appearances and depositions, do you bill at the same rate?
A. Yes.
Q. So you consider that consultation also?
A. Yes.
Q. You indicated that you do consultation to industry.
A. Yes.
Q. Would that be petroleum and chemical industries?
A. To some extent, yes; predominantly

pharmaceutical industry.

Q. Are you doing any current consulting work with any of the individual petroleum or chemical companies?

A. Not to my knowledge.

Q. Okay. How many people work with you?

A. In my laboratory?

Q. In your lab, yes.

A. Seven to ten.

Q. Is anyone else in your laboratory actively seeking grants or research?

A. No.

Q. So everything would come in through you?

A. Yes.

Q. If you could estimate for me, what percentage of your professional time is devoted to litigation matters?

A. It's less than 10 percent. It's roughly between say 7 and 10 percent.

Q. If I asked you the same question, what percentage of your gross income would be derived from litigation matters, would it be in the same range?

A. No. If I look at consulting as a

whole, it's roughly half of my income, maybe slightly more.

Q. That would be litigation-based consulting work?

A. It would be litigation. It would also be pharmaceutical. It would be everything that I do that involves compensation. Advice to regulatory agencies, virtually all my consulting activities.

Q. What I was trying to do, though, is break out from that the litigation. Can you do that right now?

A. Between 60 and 70 percent, probably.

Q. Of that would be litigation?

A. Yes.

Q. So 60 to 70 percent of the 50 percent would be the litigation-based consulting work, as you are calling it?

A. Yes.

Q. And that would be on an income basis, gross income?

A. Yes. These are rough figures, believe me.

Q. Can you characterize the amount of weight you would place in epidemiology as opposed

to, as you are calling it, mechanistic type studies, with regard to forming an opinion in this case?

A. That answer depends on a number of factors. As I mentioned before, if you have human data, I think you should use it.

But by the same token, epidemiology studies are extremely hard to control. They are extremely hard to use in a manner that gives you a definitive answer to your question. It's not like a hypothesis-driven exercise in the laboratory, where you can control all of the parameters that go into it. So epidemiology is a lot more difficult as a tool, but again, it deals with humans.

I tend to view epidemiology studies in an area as a whole, as opposed to taking individual studies and arriving at an opinion based upon a single study, and that's because I don't find very many epidemiology studies to be definitive. You have to look for a pattern.

On the other hand, it is possible, if well done, to obtain definitive answers with experimental studies, but they tend to have a much narrower scope and they are much more focused.

Q. By experimental studies, do you mean

something like an animal study or a --

A. Either an animal study or a study using tissues from either animals or humans.

Q. Which is what you are engaged in with the bone marrow and what have you?

A. Yes.

Q. By "narrower," you mean focused in on a specific cell or a specific area of the body as opposed to a more sweeping conclusion of occurrence of disease?

A. Yes. I think that these types of studies are very valuable as tools with which to test the validity of assumptions that are raised in epidemiology studies.

Q. Is there any particular epidemiology that you are relying on in support of your opinions with regard, first of all, to benzene and the occurrence of Mr. Stelly and Mr. LeBlanc's diseases?

A. Yes, and I have brought copies of those studies with me.

Q. Okay. So the list of epidemiology that we have in Section 1 of Exhibit 5, I think it is, the Tabershaw report from '74, the Rinsky studies, '81, '87, some of Dr. Wong's materials are in

there. Is there anything else that you would point to in the realm of epidemiology that you are relying on?

A. Rushton and Alderson.

Q. Would that be the '83?

A. Yes. And when you say "rely on" I would like to qualify that.

Q. Sure.

A. I don't rely on any individual article totally. I evaluate it for what I consider are its strengths and weaknesses and I arrive at an opinion, but that does not mean that, in the sense of relying on everything in an article or a report as being accurate or that I agree with, I don't rely on individual papers in that manner.

Q. Do you perform your own what I will call meta-analysis when you look at the sum total of the epidemiology in the area?

A. Meta-analysis has gotten to be a buzzword. To the extent that it allows one to take a number of different studies and evaluate them as a group, it is a valuable tool.

But by the same token, I don't think that it requires a meta-analysis to see the obvious; therefore, if you have consistency within

a series of epidemiology studies, each of which brings to the arena their own strengths and weaknesses, I don't think you necessarily -- from my own point of view, I don't need a meta-analysis to reach an opinion.

Where I think a meta-analysis is useful is where you can't do that, but that has not been my problem in this particular case.

Q. Consistency being report to report to report?

A. Yes. As I said before, an individual epidemiology study to me is rarely definitive. You really have to look at the sum total of literature that's there in arriving at an opinion, and you look for a pattern, whether there is a consistent pattern.

One problem associated with controlling epidemiology studies, especially if you are dealing with a broad segment of the population, is ascertaining what's a negative result, and whether or not there is a causal association between an alleged exposure or a hypothesized exposure or occupation and a given finding.

If in fact there is such a relationship, one should expect to see it

repeatedly and see it over and over again, and you see a pattern established across a variety of studies with different populations.

Q. With regard specifically now to multiple myeloma, can you characterize the, for lack of a better word, rareness of that disease process in the general spectrum of the population?

A. Yes. It is by no means an esoteric or rare tumor type. It occurs approximately, and this will vary depending upon who you read and what study you look at, but my best recollection is the last figures that I have seen, it accounts for approximately 1 percent of human cancers. And it probably represents somewhere between 10 and 20 -- probably not 20, it's probably 10 to 15 percent of hematopoietic and lymphoid neoplasms.

Q. Generally, the other diseases that would fall into that category would be what?

A. Leukemias, hematopoietic lymphomas. That would be it.

Q. So it would be you said 10 to --

A. I would say it's going to be somewhere between 10 and 15 percent.

Q. Of all those diseases?

A. Yes. It's definitely an age-related

disease, which makes it somewhat difficult to evaluate incidence in certain cases.

Q. That was the next area of questioning. I was wondering how, in an epidemiological sense, you can get the degree of consistency in findings that you need to form a conclusion that the epidemiology is proven as to causation with a rare disease.

MS. ARRAS: I am going to object to the form. He has just testified that it's not rare.

MR. SPEARS: That's correct.

BY MR. FLERLAGE:

Q. Let me try again. Is there enough multiple myeloma to form an opinion based on epidemiology alone as to causation?

MS. ARRAS: I am going to object to the form. Are you asking just generally?

MR. FLERLAGE: Yeah.

MS. ARRAS: In a hypothetical, not specific to any disease process?

MR. FLERLAGE: Yes.

A. Could you repeat the question, please?

Q. Is there enough incidence of multiple myeloma in the population as a whole to form

conclusions based on epidemiology as to any causation?

A. If you were to ask me that question in the mid '80s, I would have said no. Having reviewed the literature again at Ms. Arras' request in preparation for this case, I am satisfied that there is a sufficient literature base to reach that conclusion.

Q. And that's based on your current review in these two cases?

A. Yes.

Q. Had you performed such a review prior to your testimony in the Ellis case?

A. No. As I said, the last time I visited the issue of multiple myeloma was in the mid '80s, and I haven't taken a serious intensive look at that literature prior to preparation for this case.

Q. Well, limiting this question to one of those esoteric diseases, whatever it may be, very rare, extremely rare in incidence, is epidemiology a useful tool in determining cause and effect in the context of such a disease?

A. Actually, it is. That's because if a disease is so rare that you see extremely few cases in the general population, then when you begin to

see cases occurring, your attention is immediately drawn to the fact that there may in fact be a common etiology. So rarity is not always a handicap. It can in fact provide a useful indicator.

Q. Is the concept of confidence intervals, the 95 percent and the range of the interval, does that increase with the degree of rarity of the disease?

A. It's going to depend on the power of your study. I mean it's not just the incidence of the disease. It also depends upon your study group, how it's designed and what the questions are that you are asking. You have to look at both sides of the equation to determine what goes into determining the probability of a finding or seeing a difference between two compared populations.

Q. Doctor, at what point in time did epidemiology become a useful tool in determining cause and effect as a science? Can you answer that?

A. I am not sure I understand the question. If you are talking about the very first occupational disease that was ever recognized as such, most texts refer back to scrotal cancer in

chimneysweeps in England. It's standard academic fare for introducing the topic of epidemiology.

Q. And that would have been how long ago?

A. We are talking about 100, 150 years.

Q. Doctor, have you discussed either your research or your opinions in this particular case with any other individuals, any other experts, I should say?

A. I have had a brief conversation with Dr. Wong and Dr. Bickers in this case.

Q. When did you talk to Dr. Wong?

A. I believe it was last week.

Q. It was prior to his testimony? He testified yesterday in deposition.

A. Yes.

Q. And Dr. Bickers, when did you speak with him?

A. Same time.

Q. Did you have a conference call type arrangement?

A. I believe so, as I recall.

Q. Was it in conjunction with any attorneys?

A. Yes, Ms. Arras.

Q. Ms. Arras? Okay. At that time,

generally, did you discuss each others' opinions?

MS. ARRAS: I am going to object. We have established the fact that there was a conversation, and I think if we get into any of the substance of it, we are treading very close to work product. You are going to have an opportunity to question Dr. Bickers. I don't know if you are the person taking the deposition, but his deposition is scheduled for Friday. You can obtain his opinions at that time. You have Dr. Irons' and Dr. Wong's.

BY MR. FLERLAGE:

Q. Are you basing any of your conclusions or opinions in this case on any conversations you may have had with any other expert?

A. No.

Q. So whenever this conference call occurred, a week or a week and a half ago, whenever it was, your opinions today are not based on anything that was derived from that?

A. Let me clarify that. I have obtained one or two pieces of information with respect to Dr. Wong's own studies that have been useful to me,

but I wouldn't say that they played a substantive role in my reaching my opinion.

Q. Can you categorize the bits of information you received from Dr. Wong?

A. Yeah. I asked him for clarification as to some of the data that he presented in one of his papers.

Q. And is that paper in your Exhibit No. 5 materials?

A. Yes.

Q. And which one was that?

A. The 1986 petroleum refinery study.

Q. Okay. And what information did you ask him?

A. I asked him for a breakdown of what multiple myeloma incidence was relative to other lymphoid neoplasms, and he told me.

Q. Have you discussed the cases, meaning Stelly and LeBlanc, with any other consulting or non-consulting experts?

A. No.

Q. Since December, I guess -- I think you talked about this briefly. Since December, have you been deposed in any other litigation matters?

A. Yes, two.

Q. And do you remember the case names?
A. Albertson versus KNE Energy in June, and Conde versus Velsecal in August.
Q. Were they chemical cases?
A. Yes.
Q. What types of substances were involved?
A. The allegation in Albertson is benzene.
Q. Is it a leukemia case?
A. No. I don't know what kind of a case it is. I am still trying to find out what the diseases are.
Q. And this is after your deposition?
A. That's right.
Q. How about the other case?
A. There are no leukemias in the Albertson case, I can tell you. Conde versus Velsecal is chlordane, and it's a variety of allegations related to health effects, none of which are leukemia.
Q. May I ask you what your opinion was in the first case?
A. That the levels of benzene to which the plaintiffs were exposed does not constitute a measurable health risk, and in -- do you want to know the second one?

Q. Let me ask you a little bit about that. Was that based on personal monitoring or some other information you had about the actual exposure levels?

A. The exposure levels -- it's a water case basically, and the exposure levels have been measured, or the water levels have been measured by EPA.

Q. Okay. In what context was there water exposure?

A. Well water.

Q. Okay. With regard to the other case, what was your opinion? That would be Conde?

A. Yes. Basically that the allegations of the plaintiffs with respect to health effects were not related to chlordane exposure.

Q. Okay. Have you ever either been retained by or testified on behalf of a plaintiff?

A. I have been retained by three plaintiffs. I have not testified on behalf of a plaintiff.

Q. Could I ask you then what percentage of your total litigation work has been defense retention and testimony?

A. Probably 80 to 90 percent.

Q. About how many litigation cases do you take per year, if you can average it out?

A. I prepared, as best as I could, a list of the depositions and trial testimony that I have given.

Q. And this starts in 1988?

A. Yes. That's the best of my recollection, because I don't keep those records. I just put that together in response to this.

Q. And this is, again, based on your recollection, without referring to any specific materials?

A. Yes.

Q. Did your litigation-based consultation begin then in 1988?

A. Yes.

Q. And this is the testimony only; it doesn't include the cases where you were retained and did not testify?

A. That's correct.

Q. Could you give me an estimate of how many additional cases there are under that category?

A. That would be -- I really don't have a clear idea on that, because it's very difficult for

me to keep cases straight. Sometimes they are put together; sometimes they are split up. I think more in terms of issues than cases.

As I said before, it represents about 7 to 10 percent of my time. That's about as good an estimate as I can give you.

Q. Okay. I guess I had better put a tag on this.

(EXHIBIT NO. 7 WAS MARKED)

A. It's highly variable.

Q. Do you have any records at all that you keep, routine business records which would indicate the number of times you have been retained?

A. No.

Q. What kind of bookkeeping do you use to keep track of where you stand with litigation matters?

A. You are looking at it.

Q. So that all comes from up here, right, indicating your head?

A. If I keep a piece of paper on a particular case, when the case is concluded I throw the paper away, along with virtually everything else that I receive; otherwise I would be buried in paper.

Q. So you don't keep the depositions or anything?

A. No.

Q. Referring to Exhibit 7, is there any way you can break down the cases in terms of either disease process or chemical involved? I should say chemical or causative agent.

A. Chronic myelogenous leukemia, benzene; acute myelogenous leukemia, benzene.

Q. When you say AML and benzene, are you talking about the second case there?

A. Yes.

Q. Okay.

A. Chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and angiolymphadenopathy. The allegation there was benzene.

Q. Are we on the fifth one now?

A. Fourth one. Chronic lymphocytic leukemia and benzene.

Q. That would be the fifth one?

A. That's the fourth one.

Q. Okay.

A. Chlordane and rash, eczema. Excuse me. I take it back. I have testified in a plaintiff's case. That makes four plaintiffs' cases.

Q. Which one was that?
A. Anschutz versus National Lead, and the issue was lead contamination.
Q. Water? Airborne?
A. Ground.
Q. Ground?
A. Chronic lymphocytic leukemia, and I think it was butadiene; could have been benzene, could have been both.
Q. Which case is that?
A. Chambers. Myelofibrosis and butadiene; non-Hodgkin's lymphoma and benzene; benzene and a variety of complaints that could best be described as immune dysfunction. I even hate to say the word.
Q. Which case was that?
A. Albertson versus KNE. And as I mentioned, Conde was chlordane and a variety of complaints.
Q. Was your opinion in each of those cases, save for the Anschutz case or the lead case, that there was no relationship between the disease process and the alleged causative agent?
A. Yes. Excuse me. That's not entirely true. For AML and benzene, that is not my opinion.

Q. So you find there is a causal connection between AML and benzene?

A. Benzene exposure, high levels of benzene exposure.

Q. High levels only?

A. Yes. It's a dose-related phenomenon.

Q. Would the dose be dependent upon the intensity of individual exposure or the duration of exposure or both?

A. Both.

Q. Let me ask you as a group. In your opinion, would benzene, butadiene, ethylene oxide -- and I will limit it to those three for this deposition -- be classified as carcinogens?

A. They would all three be classified as animal carcinogens.

Q. In the human context, would they be classified as carcinogens?

A. Benzene is classified as a human leukemogen. The other two are not.

Q. Would that represent a presently existing conclusion based upon the state of the research into butadiene and ethylene oxide as far as causation is concerned?

A. Certainly in terms of my opinion,

that's the case. As far as what they are classified on by other agencies, I think it's fair to summarize the state of the art in that since there is sufficient animal data for butadiene, and arguably sufficient animal data for ethylene oxide, that they would in regulatory terms be classified as probable or suspect human carcinogens, simply because there is sufficient evidence in animals.

Q. So you are talking about as far as OSHA or EPA would be concerned?

A. EPA, not OSHA.

Q. And that would be your understanding of how they would characterize butadiene and ethylene oxide?

A. Yes.

Q. Is benzene a complete carcinogen in terms of leukemia or bone marrow processes?

A. I believe the term is misleading, an oversimplification of the case, but in the context of chronic exposure to benzene, by itself, lead to the development of AML, the answer is yes.

Q. Are you limiting that solely to AML?

A. Yes.

Q. It doesn't move to CML; it doesn't move to any of the other leukemias?

A. There is no evidence to support that.
Q. Okay.
A. Obviously there are several variants of AML that are included in that grouping. When I talk about AML, I am talking about the major variants of AML as well, for the most part.
Q. And I think early on we established your opinion, but let me get it again. Any of the three chemicals, benzene, butadiene and ethylene oxide; what's your opinion to a reasonable degree of scientific certainty as to whether or not they are capable of inducing a multiple myeloma in a human being?
A. There is not sufficient scientific or medical evidence to support that conclusion.
Q. Would you consider butadiene or ethylene oxide to be a promoter of a multiple myeloma?
A. No. I think that's a misstatement. There are no initiation-promotion paradigms for any leukemia or lymphoma model in man or experimental animals. If you look at the characteristics of the promoters that have been studied in typical liver and skin tumor models, these compounds don't have any of the characteristics of promoters. There is

no evidence to even, I think, support any speculation of butadiene as a promoter.

Q. Okay. Is butadiene known to cause any disease in man?

A. No.

Q. Is ethylene oxide known to cause any disease in man?

A. It can cause toxicity, especially at high doses.

Q. Toxicity would be a non-malignant type reaction?

A. Yes.

Q. Would that be liver toxicity?

A. To the best of my recollection, acute exposure may cause some respiratory distress. It's going to cause some hemolytic anemia and some problems associated with red cell function and metabolism. It will lead to an anemia.

Q. Would it be your testimony then that butadiene is not a potentially harmful substance when it results in exposure to human beings?

MS. ARRAS: I am going to object to the form.

BY MR. FLERLAGE:

Q. If you can answer it.

A. As a toxicologist, I don't think there is any non-toxic substances. I think everything is toxic, including water. It depends on root. It depends on dose. It depends on the specific condition under which the exposure occurs.

I think that the epidemiology associated with butadiene toxicity in man, especially as it relates to carcinogenesis, is inconsistent. It is confusing. It is inadequate, and it does not establish a clear pattern of anything, which is what I think the state of the art is today.

Q. Do you intend to speak to state of the art in terms of when it was known or when it should have been known within industry that benzene was a potentially harmful substance?

A. A potentially harmful substance?

Q. Yeah.

MS. ARRAS: I am going to object to the form.

A. As I said before, I think everything is a potentially harmful substance. It's a matter of dose. It's a matter of root. It's a matter of regimen. From that standpoint, it becomes -- I find it difficult to answer your question globally.

Q. Are you familiar with the API report on benzene, which came out in 1948 I believe?

A. I am sure I have seen it.

Q. Okay. If in that report benzene was described as a toxic substance, would that indicate a certain state of knowledge of the API with regard to the potential harmful effects of exposure to benzene?

A. First of all, I wouldn't consider that document to be authoritative with respect to the science. Second of all, I think it's clear that throughout the '30s, '40s, '50s, and even the '60s, there is a body of literature that grew to indicate that benzene in high concentrations caused blood dyscrasias, bone marrow suppression, aplastic anemia, thrombocytopenia, a variety of abnormalities associated with that. I don't think that's an issue. The issue is the dose and what those abnormalities were.

Q. Is that a sufficient body of information to cause a reaction among industry members to take precautions against potentially toxic exposures to benzene?

A. I think that if you have knowledge of potential toxicity associated with any exposure

scenario, regardless of whether it's benzene or anything else, that it is prudent to take steps to limits those exposures. The question is one of threshold and one of dose.

Q. Are you aware of what steps were taken by industry in general to determine what the toxic levels of benzene exposure would have been in let's say the '30s and '40s?

A. I am aware of literature. Other than that, I am not aware of anything besides what appeared in the published literature.

Q. And what published literature are you referring to, if you can be specific at all?

A. The sum total case reports, isolated case reports, as well as the collections of cases and the epidemiology studies that followed them.

We are not talking about a specific point in time when recognition of toxicity occurred. Science doesn't work that way. I think it's fair to say that by the '60s, there was an appreciation that benzene could cause bone marrow suppression. That's the sum total accumulation of a lot of different reports in different publications.

Also, the whole process of recognizing

the toxicity of benzene and what its potential toxicity was coincided with an increase in sophistication in hematology in general.

Q. I don't want to put words in your mouth, but are you referring to individual case studies of the incidence of leukemia and benzene-exposed populations during the 1930s and '40s when you talk about existing bodies of literature?

MS. ARRAS: I am going to object to the form.

A. There are isolated case reports which began to appear in the '30s. The very first controlled study that was ever done, and it's by no means a paradigm of experimental design, is a study by Goldwater, et al, looking at the lithography industry in New York. That was 1939-1941. That study demonstrated that under high levels of exposure, benzene could cause bone marrow suppression.

And as I said, without referring back to the literature, I can't tell you the specific number of cases, but there were cases reported by Hunter. There were cases that were reported earlier than that, one or two here and there, a

handful, and that continued up through the '60s.

An individual case doesn't really provide you with I think sufficient information to draw a conclusion. All it can do is draw attention to a potential problem. Certainly by the mid '60s, there was reason to be concerned about high-level exposure to benzene.

Browning, in 1965, published a collection of cases that certainly was not definitive or controlled, but provided sufficient evidence that there was something to be concerned about and that it should be studied.

About the same time, the late '60s, we have studies coming out of Italy and Turkey. Vigliani published a collection, again, of cases; not controlled, but nevertheless pointing a finger at benzene and high-level exposure in terms of -- now we are talking about not only bone marrow suppression, but also leukemia.

The issue of bone marrow suppression I think is one that people began to realize was a problem somewhere between the '40s and the '60s. Certainly by the mid '60s it was established.

Q. As a toxicologist, given an understanding of potential danger to high-level

exposure to benzene, what in your opinion should have been done to protect people exposed to high levels of benzene in industry?

MR. McCALL: I am going to object to the form of the question, Counsel, as overlybroad. I mean the use of the term "industry" without any further definition and identification of what people you are talking about, I think that's just objectable as to form

MR. SPEARS: I would echo that, and also you didn't qualify it as to what point in time we are talking about. 1990s? '80s? 1800s? What are we talking about?

MS. ARRAS: I also object that it's beyond the scope of the witness' expertise.

BY MR. FLERLAGE:

Q. Can you answer it?

A. Could you state the question again?

Q. I think I better have it read back.

(RECORD READ BACK BY REPORTER)

A. As a toxicologist, I am neither an engineer, nor am I an industrial hygienist, so I

cannot speak to specific measures that should or should not be taken. But I think that the basis of your question -- your question formulates the basis of my answer, and that is to eliminate high-level exposure. I mean it's not rocket science.

Q. Okay. Exposure; we keep talking about exposure. What are the methods by which persons can become exposed to benzene?

A. Certainly at high levels or significant levels, exposure is usually associated with contingent events, whether they be fugitive emissions or spills or leaks or misuse of the chemical. Certainly in terms of cumulative risk assessment, there is a great deal of concern in many circles today over a chronic level of exposure from water or air, cigarette smoking, a variety of other sources.

Q. Bottom line is you either breath it in or you absorb it through your skin or you ingest it somehow?

A. Those are the principal routes. I think that under most circumstances the major root for significant absorption of benzene is inhalation. Even in the context of skin exposure, the situation almost always favors inhalation as

the major root.

Q. Are benzene metabolites created by the body within the lungs and the liver?

A. Predominantly the liver. One could argue or speculate as to the role of the lung, but I think the liver is by far the most important.

Q. And the roots by which benzene reaches the liver would be any of the three that we have talked about; that would be ingestion, absorption or inhalation?

A. Yes. There are some differences. Obviously, in terms of those roots, there are some subtleties. But certainly in the case of inhalation, the liver is the principal metabolic organ, and even for ingestion, you are going to have a first pass effect, but still, the liver is going to be the first order.

Q. Is there any indication that the bone marrow itself creates the metabolites that cause the damage done in the bone marrow? And I am talking about benzene right now. In other words, does the benzene itself, as benzene, reach the bone marrow, and can it be metabolized therein?

A. I have done some early work looking in rats with respect to the innate ability of the bone

marrow to metabolize benzene, and if my recollection is correct, it's on the order of 1/10,000 of a percent of the rate of metabolism that goes on in the liver.

I think there is some evidence to suggest that you can actually measure benzene metabolism detected in human bone marrow. But by the same token, that's not been really thoroughly studied, and one of the reasons is because it is such a minor source for metabolism. Certainly in all the studies of toxicity that I am aware of, the influence of metabolism on toxicity is due to the liver.

Q. Okay. The reason I asked those questions is I wanted to find out if there is a difference or if it's understood that there is a difference between the way butadiene and/or ethylene oxide would be metabolized by the body.

A. Well, I haven't really finished benzene yet.

Q. I'm sorry. Go ahead, any way you want to answer it.

A. You are dealing with a very complex issue. In the case of benzene, primary metabolism occurs in the liver. This is a detoxification

process primarily.

At the same time, you have secondary metabolism at the level of the bone marrow, and I think tertiary metabolism at the level of the bone marrow. This is very important, because in the absence of that metabolism you are not going to get the pattern of metabolite accumulation in the bone marrow that you do, which makes the bone marrow a target for benzene. And it's those secondary metabolites and that secondary, tertiary metabolism that's important.

In the case of butadiene, we have evidence to suggest that butadiene is metabolized, certainly in the mouse, in both the liver and the bone marrow. It may be metabolized in other organs as well. It is not metabolized by the same enzyme systems per se. It's a totally different animal with respect to metabolism.

Ethylene oxide is a direct acting compound and does not require metabolism to produce toxicity directly. What that means is, obviously, if you get ethylene oxide to a site, it has the potential to react with those molecules, but there are a sea of molecules it's going to encounter en route, and so the primary effects of ethylene

oxide are going to be more proximate than the primary effects of butadiene or benzene.

Q. Would the butadiene and/or ethylene oxide metabolites, which in the case of at least ethylene oxide do happen to reach the bone marrow, assuming they did, would they react on the same cells that the benzene metabolites react on, initially?

A. It's not so much a function of reaction on -- I mean if a compound is present and a cell is present, there is potential for a reaction. But in general, when you look at differential toxicity, what you find is it's the susceptibility of individual cells and their capability to either activate or detoxify that molecule that determines their susceptibility and what the pattern of toxicity will be. It just isn't simply getting a molecule to a given cell. That plays a role, but it is only one step in the process.

Q. Am I given to understand from your testimony that detoxification is more complete in the cases of butadiene and ethylene oxide than it would be in the case of benzene?

A. No, not -- it depends upon what question you are asking. I am saying that the

delivery of a molecule that can react potentially with a cell to a given cell is dependent on, one, its initial reactivity. If I mean if it's so reactive -- if you, for instance, inhale an extremely -- let's take hypothetically a very reactive molecule, and ethylene oxide is certainly a reactive molecule.

To speculate on its reaching a site such as the bone marrow in sufficient concentration to produce toxicity is a much greater reach than it is for something like benzene, where benzene itself is not toxic, except when it becomes a solvent, in extremely high concentrations. It has to be metabolized in the liver. The metabolites are relatively stable. They can be transported to the bone marrow, where they can undergo secondary metabolism to form highly reactive metabolites that are not stable and can't move around.

As I said, it becomes a very complex issue, and it's hard to generalize. If you ask a specific question, I can do any best to address it, but it's hard in global terms to describe individual features that will allow to you predict the toxicity of a given compound.

Q. Let's put it in terms of leukemia, AML;

does ethylene oxide, in your opinion, cause leukemia?

MR. McCALL: Are you saying "AML"?

BY MR. FLERLAGE:

Q. Let's make it AML.

A. I think the evidence for ethylene oxide causing leukemia in man is insufficient and contradictory. We have some relatively small studies, actually very small studies, that don't really evaluate exposure well, certainly in the initial case, and that are not very well controlled, that have an extremely low incidence. In fact, I think we are talking in the initial paper approximately one leukemia and one lymphoid neoplasm that was reported.

And on the other hand, we have a study by Morgan which basically refutes that, that finds no relationship between ethylene oxide and hematopoietic or lymphoid neoplasms. We have confounding exposure scenarios, certainly in the first case, and on the basis of that literature I don't think you can draw a conclusion that in fact ethylene oxide is associated with hematopoietic or lymphoid neoplasms.

Q. That's based on epidemiology, though?

A. Yes. It's not based on mechanistic studies of either animals or human experience?

A. I think the animal studies don't help us, certainly not to date. I don't think they allow us to draw that conclusion or to support or refute the epidemiology.

In order to do mechanistic studies, you have to frame a fairly well-focused hypothesis, which means you have to have a relationship that you can then test. I don't think the epidemiology studies bring us to that point with ethylene oxide.

(OFF THE RECORD DISCUSSION)

BY MR. FLERLAGE:

Q. I do want to try and ask you that same question, limiting it to AML. Does butadiene cause AML?

A. I don't think that there is sufficient evidence to indicate that it does. I think you have very conflicting literature base. You have an initial study that did not have sufficient power to answer the question, but suggested there might be an increase.

You have got other studies that actually see a deficit of AML. You have got a study that saw no increase in AML in a

retrospective cohort, and then perhaps an increase in a subpopulation in a case-control.

Based on the power of that study, those two findings are inconsistent, and probably have to do with problems of assignment in exposure category. At the present time, I don't think there is sufficient pattern or consistency in the epidemiologic literature to say anything about butadiene.

Q. Is there a sufficient mechanistic study of the metabolic processes of butadiene to arrive at a conclusion as to whether it's metabolized the same way as benzene is?

A. It's not.

Q. In what ways is it different?

A. Well, it doesn't form the same molecules. It has a totally different metabolic pathway.

The initial metabolism of butadiene involves the primary hydroxylation or epoxidation to form a monoepoxide, epoxibutene. Secondary metabolism after that I think is not at all well characterized. I think the literature that's out there to date is probably, for the most part, erroneous with respect to the role of secondary

metabolism of butadiene, and that is part and parcel of what we are researching at the present time.

Q. So there is no determination, no conclusion as to whether the metabolites of butadiene are capable of reaching the bone marrow; is that the idea?

A. No. I think that there is certainly evidence in the mouse that the primary metabolite does reach the bone marrow, and it does produce some relatively specific effects on bone marrow cells. We haven't completed those studies, but it certainly looks as though it has some effects. They are totally different than benzene.

Q. In other words, the effects are totally different than benzene?

A. The cell types and the responses that are seen in those cells are different. And certainly from a mechanistic standpoint, butadiene and benzene are not mechanistically linked.

Q. Okay.

A. So I would not, as a matter of fact, expect to see the same pattern of toxicity in man.

Q. Okay. Doctor, from your review of the information that you received from counsel with

regard to the employment backgrounds of Mr. LeBlanc and Mr. Stelly, do you have an opinion to a reasonable degree of scientific certainty as to whether, first of all, Mr. LeBlanc was exposed to benzene during his career?

A. Could I see my notes?

Q. Sure. Help yourself. Here they are right here.

A. Well, to clarify, let me clarify one issue. Benzene is ubiquitous. If you are going to talk about exposure, we have all been exposed.

Q. How about occupationally exposed?

A. I have no information that's been provided to me that would lead me to reach a conclusion as to any exposure to benzene from an occupational standpoint.

Q. Either way; he was not or he was?

A. That's correct.

Q. Would the same be true then in Mr. LeBlanc's case for butadiene and ethylene oxide?

A. Yes. To the extent that I find no -- there is no evidence that I have seen in terms of their depositions that allow me to reach a conclusion that they have been exposed to

significant levels of these agents.

Q. That would be all three of the agents; benzene, butadiene, ethylene oxide?

A. Yes.

Q. Is there information which would lead you to conclude that Mr. LeBlanc was not exposed to any of the three substances?

A. Again, you can't prove a negative, certainly from a scientific standpoint, so I am certainly not going to generalize that they have never been exposed to these agents. I just said, for instance, that everyone has been exposed to benzene. Everybody has mostly likely been exposed to ethylene oxide. The only one that I would say there is not a great deal of opportunity for exposure in the general population is butadiene.

Q. Doctor, to the best of your knowledge, was Mr. LeBlanc's case originally in with the Ellis group?

A. I have no idea.

Q. There was one thing in this deposition that was puzzling to me.

MS. ARRAS: Perhaps we could clarify; that was Maxie LeBlanc.

MR. FLERLAGE: That was a different

LeBlanc?

MS. ARRAS: Yes.

MR. FLERLAGE: Oh, okay. Thank you. So there were two LeBlancs we are talking about then. It wasn't on the caption anywhere, and I just didn't know.

BY MR. FLERLAGE:

Q. Okay. In Mr. LeBlanc's case, from the information you received either from in his deposition or from counsel in summary form, can you tell me where Mr. LeBlanc was employed, where he would have been exposed occupationally to benzene or potentially could have been exposed to benzene?

MS. ARRAS: I believe the doctor has testified that he doesn't see the evidence of exposure to benzene in the records, so therefore it would be difficult for him to answer where he thought there was exposure.

BY MR. FLERLAGE:

Q. Is that a fair summary of what you said, Doctor, that you can't find any evidence that he was exposed to benzene?

A. I don't find any evidence that would

lead me to be able quantify or qualify his exposure to benzene in an occupational setting.

Q. Well, that's different than counsel just said, quantify or qualify. Quantify means put a number on the level of exposure?

A. Or make any statement whatsoever with respect to whether it was a little, none, trivial, a lot, more. I mean there is just no -- I have no data.

Q. What was Mr. LeBlanc's trade?

A. He was involved in construction, primarily roofing, both resident and commercial. He did some carpentry, but not in the context of working in commercial plants. He worked in pipewrapping and in roofing for various periods of time.

His exposure history with respect to -- occupational history with respect to the petroleum industry and chemical industry appears to be primarily from 1962 to 1985. During that period of time, he worked only part-time as a contractor at those facilities, and he spent about half of his time doing roofing.

Q. Based upon your review of the records of deposition materials and other summary materials

provided from counsel then, your assessment of his potential exposure to benzene would be limited to that time period, '62 through '85? And I am talking, again, about occupational exposure. I left that out. I'm sorry.

A. I don't think that's a fair statement either, because certainly in the roofing trade, working with tar pitch, asphalt, petroleum distillates, what have you, since the '40s, the potential for exposure to a wide variety of agents, including benzene, would exist in that environment, independent of the exposure that took place or that could have taken place between 1962 and 1985.

Q. Did Mr. LeBlanc perform any pipewrapping which involved the use of asphalt at the plants, the petroleum or chemical plants that are involved in this case?

A. He described pipewrapping that involved the use of a product that required high heating in order to apply it, and I suspect that that was either a tar pitch or asphalt-based product. That's the extent of my knowledge.

Q. You wouldn't know the chemical makeup of that substance then?

A. I vaguely remember some discussion of

it in his deposition, but I don't recall at the present time.

Q. Did Mr. LeBlanc do any asphalt-based roofing or tar pitch-based roofing at any of the chemical or petroleum plants involved in this case?

A. That is my understanding.

Q. And what then is your understanding of the type or extent of such work that he did at these plants?

A. Again, it's very vague, but my recollection is that it was approximately 50 percent of his time.

Q. Are you able to conclude from the, as you describe it, I guess limited information that you have got on exposure that Mr. LeBlanc's exposure to asphalt or tar pitch during those periods of time that you have described was a potential cause of his disease process?

A. I think the sum total of epidemiologic evidence with respect to occupational exposure and multiple myeloma allows one to make a clear assignment of causation to radiation exposure, gamma radiation.

I think that as of today, there is probably sufficient evidence to link farming and

work with animals to multiple myeloma. When you get beyond that, you get into the area of hypothesis, where there have been various relationships suggested in various studies, others in others, and you have an inconsistent database with respect to the relationship between exposure in a given situation and development of multiple myeloma.

I would say that with respect to the hypothesis that benzene causes multiple myeloma or that exposure to benzene does, and the evidence to support that, there is such just as much evidence to link exposure to coal tar-based products; asphalt, pitch.

There is actually evidence in the literature to suggest that exposure to vitamin C or laxatives actually has a higher association or a greater association with multiple myeloma than benzene.

I think it's arguable for any of these various hypotheses whether there is a causal relationship. It's the weight of the evidence and the quality of the evidence, and I don't think the evidence supporting benzene is any stronger than the evidence supporting coal tar or the evidence

supporting a variety of other alleged potential relationships.

Q. Is there in there any evidence that Mr. LeBlanc used laxatives regularly during his life?

A. I don't recall any information on that from his record.

Q. Is there any evidence in the case that Mr. LeBlanc was exposed to radiation during his career?

A. He was exposed to radiation therapy after diagnosis, but I have no knowledge of radiation exposure prior to that.

Q. Okay. Is there any way you can arrive at a conclusion that the combination of his exposures that we have described, whether it be coal tar or tar pitch or asphalt and benzene, while working at one of these plants, the combination of those two, may be causative or the combination of those may act synergistically in causing his disease process?

MR. McCALL: Let me object to the form of the question as a mischaracterization of his prior testimony insofar as referring to

benzene as a cause.

BY MR. FLERLAGE:

Q. Let me retry the question. Assuming that Mr. LeBlanc was occupationally exposed to benzene during his career, and assuming that he was exposed to asphalt and tar pitch during his career, as you have described from the deposition and what have you, are you able to state to a reasonable degree of scientific certainty as to whether there might be a synergistic relationship between the two substances in causing his multiple myeloma?

MR. McCALL: Let me object to the form again as assuming facts not in evidence.

MS. ARRAS: I join.

A. No. It would be wild speculation to attempt to hypothesize interactions between those compounds. I don't think that the database literature with respect to epidemiology would allow you to make any association like that.

My own personal experience in the last few years with respect to mechanistic research doesn't support that either. My experience is that the responses and the effects that various compounds have on cells within the hematopoietic

and lymphoid system are highly specific, and you cannot predict interactions similarly on the basis of hypothesizing that two compounds may have the same target tissue.

Q. Now was Mr. LeBlanc a smoker?

A. I believe he was.

Q. Can you put it into packs per day or pack-year history?

A. I didn't do that.

Q. Can you remember whether or not he was a heavy smoker, moderate, light smoker, at least from what you can remember of the information?

A. No.

Q. Do you remember what tobacco products he may have smoked?

A. I believe it was cigarettes, but I don't recall specifically.

Q. Is smoking history at all important as a consideration in determining whether or not any of his occupational exposures caused his multiple myeloma?

A. With respect to smoking history, I would say that it's only important with respect to comparative exposure. If you are going to allege or hypothesize that low level or ambient exposure,

cumulative exposure to a compound such as benzene or butadiene plays a role in causation, then I think one has to take into account smoking history. In that context, smoking becomes probably the most significant source of cumulative exposure to either of those two compounds. From the standpoint of causation and biology, no, I don't think that that's an issue.

Q. Okay. I guess I better ask, to a reasonable degree of scientific certainty, do you have an opinion as to whether cigarette smoking played a role in Mr. LeBlanc's multiple myeloma?

A. I'm sorry. Could you reread the question?

Q. Let me just do it again, okay? To a reasonable degree of scientific certainty, do you have an opinion as to whether Mr. LeBlanc's smoking history played a role in the causation of his multiple myeloma?

A. For multiple myeloma, there is no evidence to support or refute that.

Q. Now you have talked about exposure to animals as being epidemiologically associated with multiple myeloma in human beings; is that correct?

A. Yes.

Q. Okay. Mr. Stelly; do you have a history on Mr. Stelly?

A. Yes.

Q. Do you find any evidence in his history of exposure to animals?

A. Yes.

Q. Is that important in your consideration of causation of his multiple myeloma?

A. I think the evidence to support association with farming, ranching and exposure to domestic animals is probably more impressive than the evidence for any of the other causes we have talked about, with the exception of radiation.

So certainly as far as assigning a potential causation or a potential cause for the development of his multiple myeloma, that certainly is one that would be high on my list.

Q. From the history you received of Mr. Stelly, and I am limiting it to work history or exposure history right now, can you tell me how long he was exposed to ranching or farming?

A. Well, from his deposition, he worked in his early years with his father on a dairy. In 1947, after graduating from high school, he was involved in ranching, vaccination, dipping cattle.

He was basically working as a rancher with cattle.

At various other times in his career he worked with animals. In 1960 to '61, he was a ranch foreman, worked with cattle. He had a horse accident in 1986, so my assumption is that he has probably spent the greater part of his life in intimate contact with animals, although the times that I have mentioned were times when he worked full-time in that industry.

Q. Can you assign a duration to the exposure to animals that Mr. Stelly would have sustained during his life?

A. Not accurately. I think it's obviously very significant prior to high school, and he worked full-time in 1947 in ranching. Then he worked again full-time in 1960 in ranching.

Q. Is that a significant enough exposure to animals to induce a multiple myeloma in a human being?

A. I think if you look at the epidemiologic literature, assigning a quantitative value to that kind of exposure is extremely difficult, because there are any number of different exposures that one could hypothesize are involved.

It's been hypothesized for years that ranching involves antigenic stimulation. It involves exposure to fertilizer. It involves exposure to feces and animals, viruses, to pesticides and a variety of other very complicated chemical exposure and agent exposure scenarios.

At this point in time, I don't think that it's possible to assign a quantitative value to a given exposure. I think all one can conclude is that there does appear to be a growing appreciation, both quantitatively as well as qualitatively, of a relationship between multiple myeloma and the farming industry, and he has been involved in that industry.

It's not trivial; it wasn't a day or a week or a month. He has had considerable experience in the ranching and dairy industry.

Q. But what I am getting at is are you going to state an opinion that his animal or farm exposure is what caused his multiple myeloma?

A. I am simply saying that if you are going to attribute a cause to his multiple myeloma, that that would be the first thing on my list. I am not prepared to say that that is the cause of his multiple myeloma.

Q. Okay. Are you able to characterize from Mr. Stelly's occupational history whether or not he was exposed to benzene during his career?

A. No.

Q. And why is that?

A. Again, there is no information, either qualitatively or quantitatively, that I have read in his deposition that would allow me to do that, and I have seen no records of potential exposure that was associated with the activities that he describes.

Q. He was a pipefitter; is that correct?

A. Yes.

Q. Was there any anecdotal information from any source which would describe the types of pipefitting work he did in the chemical and petroleum plants at which he worked?

A. Yes. He talked about cracking pipes and occasionally smelling the material that was in the pipes. But there is no way from those descriptions that you can draw any conclusions with respect to benzene exposure or what the levels might or might not have been.

Q. Did he describe working on any benzene systems at all in any of the plants? In the

pipefitting sense now I mean.

A. I would have to reread it to see if he specifically discussed benzene. I am sure he worked on pipes that had to do with various feed stocks and/or processes that may have contained some benzene, but again, drawing any conclusions as to what that exposure was, you can't do it from what I have read. I certainly can't.

Q. In Mr. Stelly's case, is there any evidence that Mr. Stelly may have been exposed to gamma radiation during his career?

A. Not to my knowledge.

Q. You also received medical records and a medical summary I believe from counsel; is that correct?

A. Yes.

Q. Do you have an opinion to a reasonable degree of scientific certainty as to whether or not Mr. Stelly, first of all, suffers from multiple myeloma?

A. He was diagnosed as having plasma cell myeloma, which I would consider multiple myeloma, same category.

Q. So you take no issue with the diagnosis --

A. No.
Q. -- of the disease process?
A. No.
Q. In Stelly's case?
A. That's correct.
Q. Mr. LeBlanc, the same questions; do you agree or disagree that he has what would be termed multiple myeloma?
A. In terms of what I have seen, again, it's multiple myeloma. I don't have any real problems with that.
Q. Will you be rendering any form of opinion with regard to a prognosis for these two gentlemen?
A. No.
Q. I have asked you a couple of questions, Doctor, about synergy or synergistic relationships. Is there any place in a discussion of multiple myeloma for the concept of synergy between various chemicals or substances?
A. I don't think we know enough about that to draw a meaningful conclusion, and it would be rank speculation. You could just as easily, for any of these issues of causation, speculate that there are potential interferences that could play a

role in protecting against the development of the disease. It's a very complicated issue that, from a mechanistic standpoint, I don't think is served by superficial speculation.

Q. All right.

A. We have no evidence to support that.

Q. Doctor, in the case of benzene and AML, at what exposure levels, if you can characterize it in any form, is benzene capable of inducing an AML in a human being?

A. I have probably been asked that many times. I couldn't count the number of times. Certainly if you look at the sum total of the human literature; epidemiology studies, case reports, which are usually not very useful, case-control or collections of cases, it's relatively well accepted, generally accepted, that exposure to benzene in concentrations of 100 ppm or greater for a significant period of time, usually on the order of years, in some cases many years, will lead to blood dyscrasias, lead to bone marrow suppression in a majority of individuals so exposed.

In a relatively small proportion of those, one will see the development of acute myelogenous leukemia or one of its variants. That

data is not controversial.

There is some evidence to suggest that exposures in the range of 50 to 100 parts per million may produce some bone marrow toxicity and might produce AML. I personally am concerned about cumulative exposures in that range, but again, we are talking threshold, so it's not just cumulative exposure. But chronic exposure in the 50 to 100 parts per million range is subject for concern.

As we go down in concentration, our data becomes much less reliable, much less sound, and much, much sparser, more sparse. There have been allegations and assumptions that exposures in the 25 to 50 ppm range may be capable of causing AML. I think the data is extremely unreliable, and it's very difficult to draw a conclusion.

I think that conclusions associated with potential causation below that are virtually speculatation. We really have no data below 10. Between 10 and 25, I think it's highly speculative.

So if you are asking me what level causes it, all I can do is really look at the strength, the nature of the evidence. 100, definitely; 50, maybe; between 25 and 10 and 50, I think the data is extremely insufficient to draw a

conclusion.

Q. When you are talking about 100 parts per million or 50 or 25 to 50 or 10 parts per million, are you talking about time-weighted averages now?

A. Okay. Certainly chronic exposure to 100 ppm time-weighted average for any length of time is a hazard. The risk is extremely high for blood dyscrasias, for bone marrow suppression, and in some individuals, there is the potential to develop leukemia.

If what you are asking me is do I distinguish between cumulative exposure and actual time-weighted average, yes, I do. Mathematically, it's very expedient, especially in a regulatory context, to discuss cumulative exposure in ppm years.

For instance, 100 ppm -- well, that's ridiculous. Let me back off. Let's take 50 ppm years or 75 ppm years. If you are talking about exposure to 75 parts per million for one year as being equal to 1 part per million for 75 years, I will say nonsense. I think 1 part per million for 75 years in no way, shape or form has been established as causal, whereas 75 ppm for one year,

I would be concerned about.

I think cumulative exposure is misleading with respect to causation. It's a much more complicated picture than that.

Q. Isn't there some evidence in research and/or in the literature that repeated smaller exposures in the context of benzene may be more dangerous than one large consolidated exposure?

A. Again, I can't make a generalization. If you want to discuss specific levels, even some of my own data suggests that intermittent exposure is probably as important as continuous. I don't think there is any evidence that a single exposure, even at high levels, has associated with benzene the development of leukemia. There is such just no evidence to support that.

I think that virtually all the cases that have been described have involved repeated exposure in high concentrations. And intermittent exposure, certainly in animals, can produce as much toxicity as continuous exposure to certain concentrations. There appears to be a threshold effect there as well, and that's in terms of toxicity.

Q. Would it be fair to say that

benzene-induced cancers such as AML would be dose-response diseases?

A. Yes.

Q. So is there any understanding of at what dose, quantifiable dose, the body cannot detoxify the benzene?

A. What you are talking about is threshold, and that's the issue we have just been discussing.

Q. Yeah. You can't put a number on that, though?

A. No.

Q. Is there any safe exposure to benzene?

MS. ARRAS: I am going to object to the form of the question.

A. Well, let me put it this way; we are all exposed to benzene in finite amounts in our daily life, and we don't all die of leukemia or AML or have blood dyscrasias, so obviously there are exposure levels to benzene that are not associated with these diseases. When you get into the issue of risk, you get into regulatory issues of prioritization of research and exposure issues that really don't have anything to do with causation.

Do I think that it's a good idea to be

exposed to benzene? No, but we are every day and have been throughout history, so I mean it's not a -- I don't think it's really a meaningful question in that context. There is obviously a level of exposure that's not associated with the development of these diseases.

Q. As a toxicologist, can you tell me what that level is?

A. I wish I could.

Q. As a toxicologist, do you take issue with the regulatory agencies setting limits for occupational exposure to benzene?

A. No.

MS. ARRAS: I object to the form.

A. No, that's a policy. That's not an issue of causation. The mandate for regulation is to set policy to provide for protection of the environment and for workers. I think that in the context of policy that standard setting is very appropriate. It does not necessarily mean that it's based on issues that are relevant to causation and in terms of a science.

Q. Let's change subjects slightly. Have you visited any of the plants which are the subject matter of these two cases?

A. No.
Q. Have you got any of the plant diagrams?
A. I don't have any. I may have seen plant diagrams in the Ellis case. I don't know if we are talking about the same facility or not.
Q. Would it be of any use to you to go through the plaintiffs' testimony in the context of piping diagrams or diagrams of locations where they may have worked in process plants?
A. Not unless I am provided with some meaningful industrial hygiene data.
Q. Such as personal monitoring?
A. Something.
Q. Exposure levels? Do you know if that information is out there at any of the plants?
A. No, I don't.
Q. Have you requested it?
A. I have asked for what information was available on exposure.
Q. Have you received any type of benzene monitoring information on any of the plants?
A. With respect to this particular case, no.
Q. Not limiting it to personal monitoring, but any type of benzene monitoring at any of the

plants at any time; do you have that information?

A. Levels?

Q. Yes.

A. Not to my knowledge, no.

Q. Do you know whether any of it exists or you just don't have it?

A. If it exists, I don't have it.

Q. To your knowledge, have any industrial hygiene studies been done of any of the plants which are the subject matter of this case which might be out in the public domain?

A. Not that I know of.

Q. From what cell does the myeloma come from which would be the multiple myeloma that we would have in these cases?

A. It's in the lymphoid lineage, and it's in the B lymphocyte lineage.

Q. And it would originate in the bone marrow; is that correct?

A. Yes.

Q. Is there a concept of biological plausibility for the connection of benzene with the occurrence of multiple myeloma in human beings?

A. I don't understand the question.

Q. Is there a concept called biological

plausibility for the occurrence of a disease; in other words, a connection between an exposure and the occurrence of a disease?

A. Can you define "biological plausibility" for me?

Q. Well, I am asking you. I mean I have seen that term in a couple of different contexts, and the context I am talking about, is it plausible for an exposure to occur and a reaction occur within the body that would result in the disease? And I am limiting it right now to multiple myeloma.

MR. McCALL: Counsel, let me object to the form. I don't understand your question; it's vague.

BY MR. FLERLAGE:

Q. Is there a difference between the way the benzene metabolites react in the bone marrow between the B-cells you have just described for the multiple myeloma and the cells which are affected which result in AML?

A. Yes.

Q. And how?

A. The benzene metabolites are known metabolites, primarily, but in concert with phenol and catechol, alter cytocon response in

differentiation in the myeloid progenitor population. It appears that they enhance recruitment of an earlier cell into the myeloid lineage and increase the number of cells that are at risk of replication error.

This is a regulatory effect, and it coincides with a cell type that has the metabolic machinery to produce those metabolites, namely peroxidates, I think. So it is a very -- the susceptibility of that population to altered regulation of growth coincides with the machinery to metabolize the metabolites of benzene to produce the compounds that do this.

The lymphoid cells do not have the same metabolic machinery, and coincidentally, at least to date, we have not seen regulatory changes in those cell types. At much higher concentrations in the metabolites, several levels of magnitude higher, we do see toxicity. So benzene metabolites will suppress lymphoid cell function at higher concentrations.

The altered regulation of the myeloid progenitor cells, in terms of their growth and differentiation, forms the basis of our theory with respect to secondary leukemogenesis, and it

corresponds not only to benzene, but one also sees it for a variety of chemotherapeutic drugs that are also known to cause AML.

We are pursuing studies in lymphoid populations, but we have to develop technologies that don't exist at the present time in order to do that. But certainly in terms of susceptibility and measurable events that occur, there are differences in the metabolism and the concentrations of these compounds that produce changes in these different cell populations.

Q. Is that based on an animal model that you are making this distinction?

A. At the present time it's based on studies involving the use of mouse bone marrow. We are in the process now of comparing human to mouse.

Q. And that would be for all of the bone marrow disease processes?

A. It would be for the types of phenomena that we are talking about now in terms of regulating progenitor cell function and differentiation.

Q. Are there different benzene metabolites that are created in the body as a result of the ingestion or inhalation of benzene?

A. Sure.
Q. Do the metabolites react the same way regardless of distinction in the bone marrow?
A. No. No, there are marked differences. Some of them are toxic. Some of them alter regulation or recruitment of cells in response to natural hormones or cytocons. Some of them don't do anything. Some of them are genotoxic; that is, they will cause chromosomal aberrations or types of changes that could lead to altered regulation of gene expression in the cells. Some of them don't.
Q. Based on your mechanical model, using mouse bone marrow to this point, do all the various metabolites that you have investigated thus far react the same way in lymphoid and myeloid cells?
MS. ARRAS: I am going to object to the form.
A. If you are asking me do all the metabolites do exactly the same thing in two different types of cells, my answer is no.
Q. What I am after is, given your models thus far, your animal models thus far, is it known whether the benzene metabolites will affect the lymphoid cells, and I am talking about the alteration process that you described, in the same

sense that they will affect the myeloid cells in causing AML?

MS. ARRAS: I am going to object to the form.

A. I think I have answered your question, if I understand. We have done over the last 15 years a series of studies that characterized the toxicity of these cells on lymphoid populations.

In the last five years, we have focused on looking at myeloid differentiation, because this is the population that is most relevant to the issue of acute myelogenous leukemia. What we have found is, whereas you can produce toxicity with some of the metabolites of benzene to lymphoid cells, and by "toxicity," I mean stop them from growing, one sees dramatic changes in the regulation of function of the myeloid cells at even lower concentrations.

Q. I don't want to interrupt you here, but I want to know is whether you have determined whether those metabolites will also do that in the lymphoid cells.

A. We have no evidence to support that at the present time. As I said, we are in the process of studying that question, but we are having to

develop a technique to do that that doesn't exist at the present time. Certainly the toxicity profile is different.

Q. Are you prepared to give an opinion, again, to a reasonable degree of scientific certainty, today based on your mechanistic evaluation of the lymphoid cells as to whether it's just not possible for the benzene metabolites to cause the myeloma?

A. At the present time, we do not have sufficient information to draw that conclusion in the way you have framed it. If I understand the line of your questioning, initially you were asking me are there differences between the two different types of cells that would be consistent with a difference in potential susceptibility, and I am saying yes, there are. There are metabolic differences, there are observed differences -- which, again, metabolic differences are very important.

There are observed differences in alterations and regulation we simply haven't seen in lymphoid models. We need to do further development on that. And there are differences in susceptibility to toxicity at higher

concentrations, so there are differences that coincide with the observed association between benzene exposure and AML in man.

Q. What I was after, though, was I guess you can't give me a yes or no to that, but are you able to say categorically that the benzene metabolites will not affect the lymphoid cells in the same sense that they affect the myeloid cells?

A. I can't say that categorically, no.

Q. This is from a report by -- I am going to read a passage here, and I will show it to you if you would like me to. I don't have a complete copy of it, unfortunately. It's from the annals of New York Academy of Science, Goldstein, "Exposure to Benzene," and it talks about the relation of benzene to multiple myeloma, and it talks about biomedical plausibility. I don't know if you have read anything by Dr. Goldstein on that or not.

MR. McCALL: Page 227?

MR. FLERLAGE: There you go.

BY MR. FLERLAGE:

Q. It's "Biomedical Plausibility." "There is a high level of biomedical plausibility supporting a causal relationship between benzene exposure and multiple myelomas. Biological

reactive intermediates of benzene are carcinogenic within the bone marrow, and plasma cells are located within the bone marrow. The basic cell type of plasma cells, the B lymphcyte, is affected by benzene and is probably the circulating lymphocytic cell found with benzene-induced cytogenic abnormalities. Thus we have a carcinogen that is specific to the organ at risk and affects the basic cell type, including producing cytogenic abnormalities."

I guess my question with regard to that, and I think you have a copy of it in front of you now, is do you agree with that statement?

A. I don't agree with all of it, no. I think there is a basic misconception that is understandable in the context of its subtlety and our knowledge with respect to the ontogeny of multiple myeloma. But the origin of multiple myeloma appears to be a cell that resides in the bone marrow and is probably -- at this point it's indeterminate, but probably somewhere between the level of differentiation of the pre B-cell, which could be considered technically one of committed stem cell population, and the B-cell.

So we are looking at an earlier cell as

the origin that he is referring to here in terms of the circulating lymphocyte, and I think that although there is no definitive pinpointing of where in differentiation this occurs, there is substantial evidence to suggest it's earlier than this particular cell that he is talking about.

Q. Now Dr. Goldstein, I think -- I don't have the date on this. I think it was written in what, 1987? Are you aware of that?

A. 1990.

Q. 1990? Based on what you have discovered I guess since 1990, are you aware of any retraction of this by Dr. Goldstein?

A. No. And I don't think that that's an accurate representation. Some of the literature to support what I have just said existed prior to 1990, but it's certainly been developing over the last several years. I am simply saying that with respect to this one statement that he made, he is not taking into account the evidence to suggest that the cell of origin for multiple myeloma occurs earlier in ontogeny than he is describing here. I think he is basically misstating.

Q. It's Dr. Goldstein's position, I understand, that he has related exposure to benzene

to multiple myeloma; is that correct, based upon both the biomedical plausibility and the human findings?

MS. ARRAS: I am going to object to the form of the question. You are asking Dr. Irons to draw a conclusion about an entire study, which you haven't laid the foundation for whether he is familiar with it, whether he has read it, and therefore whether he can draw a conclusion as to what Dr. Goldstein's ultimate conclusion was.

MR. FLERLAGE: Well, he has got it right in front of him. I guess in answering the question, he can do whatever he wants with it.

MS. ARRAS: Well, can he read it?

MR. FLERLAGE: Sure.

THE WITNESS: Well, I am going to have to take a more detailed look at this to answer that question.

(OFF THE RECORD DISCUSSION)

BY MR. FLERLAGE:

Q. To the best of your knowledge, has Dr. Goldstein linked occupational exposure to

benzene with multiple myeloma?

A. Well, I think in his concluding paragraph in this particular review -- which is again a review; it's an opinion, not a primary research article -- "Overall, these findings are not sufficient to make an unequivocal statement that benzene is a cause of multiple myeloma. However, they raise the strong presumption of such a causal link, and in my judgment, it is now more likely than not that benzene exposure is an etiological factor in multiple myeloma. This does not necessarily mean that any increase in the incidence of multiple myeloma in recent years can necessarily be ascribed to benzene use, but it does raise an issue that needs to be considered."

That's his opinion. In terms of the issues that he has raised with respect to the epidemiology and the biology, I think there are aspects that I would agree with.

There are aspects that I don't agree with. I would say that we disagree with respect to the presumption, and in fact I think that the data does not support that conclusion. We obviously have a difference of opinion with respect to the weight of the evidence at this point. We disagree

on many things and agree on many things. This doesn't strike me as anything that --

Q. Do you understand the standard in a civil litigation matter such as this to give an opinion as more likely than not?

A. Yes.

Q. Is that the same standard that you would use as a scientist in ariving at an opinion?

A. If I am evaluating a variety of different studies or a body of literature to reach a conclusion, yes. If I am looking at an individual study to determine whether it is a reliable indicator or I can draw a reasonable conclusion, I will use a 95 percent confidence interval or a higher standard. That is evaluating the validity and the scientific rigor in an individual study. But for looking at the literature as a whole, I'm applying a more probable than not, greater than 50 percent standard.

Q. Is that greater than 50 percent standard the standard that you have applied in giving your opinion that exposure to benzene does not cause multiple myeloma?

A. With the caveat that I have evaluated the strength, design, validity of the conclusions

and findings reached in the individual papers in reaching that conclusion, yes.

Q. Okay. Would it then be fair to say that it's your opinion that it's not biologically plausible that benzene will affect the bone marrow to such an extent that it can result in a multiple myeloma?

A. There is no evidence that will allow me to say it is not biologically plausible. However, there is considerable evidence to suggest -- I have got this backwards.

It is impossible to conclude that it is plausible with any kind of definition. There is considerable indirect evidence to suggest that it may not be, but the state of the art is such that I cannot definitively reach a conclusion as to its plausibility or lack thereof.

Q. Okay. At this point I am going to have to take a look at the materials.

(A NOON RECESS WAS TAKEN)

BY MR. FLERLAGE:

Q. Doctor, in the last hour, maybe half an hour, 45 minutes or something like that, I've been going through some of the materials that you have provided which are going to be in Exhibit No. 5, I

think it is, to the deposition. There is a number of epidemiological studies which are in the first section that you have identified as being supportive of your position; is that correct?

A. Yes.

Q. Can you answer for me how you went about synthesizing, if you will, materials in those reports to form an opinion?

A. Well, I classified them in terms of the type of report or study that they were. I then went through and evaluated them with respect to study population, experimental design, what criteria were used for classification of exposure or measurement of exposure, what types of comparisons were made, whether they were controlled versus general population, proportion mortality or retrospective cohort, case-control studies.

I then went through in my own mind and on paper and began to summarize those findings from one study to another and looked at the pattern of results that were seen from one study to another.

Q. Some of the studies in there find a causal connection between exposure to benzene in an occupational setting and multiple myeloma; do they not?

A. If you take an individual study, for instance, if you take the Rinsky study, the initial study saw no relationship. The followup suggested there was a relationship. If you take an individual study like that, you can say yes, that that was the conclusion of the authors of that study, but I think when you look at the design of that study, the classifications and their use of the information that they had, as well as in the context of all the other studies that I have looked at, that that's really the exception to the rule.

Q. Okay. In looking at the studies individually as you have described, are there any studies that you would care to address as having more weight in terms of your opinion?

A. Yes. You have to look at the size of the study, its power to see a change, you have to look at the design of the study and what assumptions are made by the individual investigators in conducting the study and in reaching their conclusions.

If you do that, I think that one can make some distinctions with respect to the reliability of the conclusions that have been reached. I don't think it's -- I mean I can do

that as an exercise. I don't think that in general it's as critical as it might be in some cases, because I think the predominant finding and the results, taking literature as a whole, support the position that there is no demonstrable relationship between benzene exposure and multiple myeloma.

Q. Which are the studies you were referring to that make the causal connection between farming or ranching and multiple myeloma?

A. For the most part, that comes from population-based case-control studies in which farming has been seen as being a risk factor. There are case-control studies that are related specifically to multiple myeloma.

In terms of lymphoma, there are also some that have looked at farming as an occupation that suggests a relationship there as well that are probably larger than some of these, and it's my understanding the results of a recent study that has been sponsored by NCI that draws the same conclusion that has yet not been published.

Q. Are you familiar with the statistics and the analysis of that study?

A. No.

Q. How are you aware of the report?

A. I have read about it. It's been bantered around in the popular press, but I have not yet seen it in the scientific literature.

To speak specifically to your question, the Morris study from 1986 saw an association with the exposure to fertilizers. The Flodin study, which is Swedish, found a relationship or at least described a relationship for farming as far as multiple myeloma. The McLaughlin study from 1988 found at least as high, if not higher, association between farming and say petroleum industry.

Q. There was another one that was in there that was Cuzick or something like that that you had in there?

A. Cuzick, also Eriksson. The Cuzick study, it's hard to draw any quantitative conclusions from. The conclusions of the author are that there is at least a two-fold risk associated with farming and food processing, and perhaps a risk associated with asbestos exposure. There is no way that I could put a quantitative value on this.

Q. They also found the petrochemical industry to be a potential causative factor, did they not?

A. I believe that is mentioned in there as well.

Q. With at least some of these studies which we are isolating with regard to farming or ranching or animal exposure, there is at least an underlying theme in many of the studies that exposure to petroleum products or chemical products is also implicated as a causal factor; is that correct?

A. As I mentioned before, the farming industry represents a very complex exposure scenario, and there is probably as much of a theme, if not greater theme, with respect to the hypothesis that we are looking at, antigen stimulation, potential exposure to viruses, and a variety of other confounders as well.

At this point in time, I don't know how you would go about segregating those out, but it's clear that farming shows up repeatedly. I mean the strength of the association varies from study to study, and you will see that. That's one of the reasons why I think you have to look across the board at the whole literature as opposed to any one individual study.

I don't think there is an individual

study that I can think of in this whole arena that in and of itself provides you with a definitive -- at least with me, with sufficient evidence to say yes, this is a causal relationship. You have to look at the pattern that exists, and the pattern with respect to farming is clear.

Q. Is there also a pattern, or is there not a pattern concerning exposure to chemicals and petrochemicals also, which is an underlying theme through most of the studies that you are talking about?

A. No. I think the pattern is entirely -- if there is a pattern at all, it does not support -- it's not consistent and it doesn't support a conclusion that there is an increased risk. We have varying degrees of association with chemical exposure, some of them related to aromatics, some to solvents, some to chemicals. Some distinguish between benzene, some don't.

But if you look across the board, I mean we have odds ratios and relative risks that do not provide and don't certainly suggest to me that there is a consistent pattern of increase. Some of these, there is actually a significant deficit. There is no association that can be drawn.

Q. Is there any explanation for finding a deficit in terms of disease occurrence among potentially exposed populations?

A. Well, in some cases, occasionally someone will hypothesize that a deficit in an epidemiologic study or a non-dose-response relationship may be in fact due to some what I would consider to be biologically unlikely explanation, but usually I think it's a function of the artifact of the process of the types of studies that we are talking about, epidemiology.

For instance, if you have an excess of a disease in a population that you are not studying or that you may be discounting, it may ask skew the potential findings relative to the general population or to some control. That definitely happens in proportional mortality studies, which are very unreliable for that reason, but it can also happen in a retrospective cohort study or a case-control study if it's not recognized and controlled for during the design phase of the study.

Q. Doctor, did you testify or were you invited to testify before OSHA promulgated rules concerning benzene exposure?

A. The only testimony I have made before a regulatory hearing was in '80 or '81, and it was an OSHA hearing on benzene emissions from a lake and hydride plant. I have not participated in any of the regulatory hearings on benzene per se.

Q. Are you familiar with the OSHA regulations concerning benzene?

A. Generally, yes.

Q. Have you reviewed them recently?

A. Specifically, probably not.

Q. Okay.

A. I can't recall.

Q. Are you aware of OSHA's opinion forming the basis of some of its regulation with regard to benzene, concerning benzene and its relationship to multiple myeloma?

MS. ARRAS: I am going to object to the form of the question. I don't know that OSHA can have an opinion in the sense that you are implying here. If you can answer the question --

A. She stole my answer. I don't know what you mean by an opinion of OSHA. OSHA sets standards.

Q. Are you familiar with the background

for the standards that went into the rationale for standards in terms of benzene?

A. I am familiar with the benzene literature which forms the basis for rule-making.

Q. Isn't it a fact that OSHA took the same literature that you are referring to in your Exhibit No. 5 and came to a different conclusion with regard to benzene and multiple myeloma?

MS. ARRAS: I am going to object to the form.

A. OSHA does not -- OSHA sets standards. It does not classify agents as carcinogenic or not. It promulgates rules with respect to exposure. Individuals who work for OSHA I am sure reach conclusions that form the basis for that rule-making, but again, OSHA is not an agency that to my knowledge renders opinions, but rather sets standards with respect to worker safety.

Q. Would it be fair to say then that they are very opinionated about their standards?

MS. ARRAS: I am going to object to the form.

MR. McCALL: I will object to the form also, as it calls for speculation.

MR. FLERLAGE: I will withdraw the

question. At least Dr. Wong would have appreciated that.

BY MR. FLERLAGE:

Q. I went through this with Dr. Wong, and I don't know if you are familiar with this whole thing or not, but this is the 29 CFR, Part 1910, Department of Labor, Occupational Safety and Health Administration, Friday, September 11, 1987. The part I have underlined is what I went through.

MS. ARRAS: Specifically what page? 34,479?

BY MR. FLERLAGE:

Q. Yes. With regard to that underlined section, do you agree with or disagree with the conclusion with regard to multiple myeloma and benzene?

A. I disagree with the conclusion. By the same token, this is not a scientific document. This is a statement made in the Federal Register in support of a rule-making in which OSHA is clearly faced with providing appropriate cost benefit analysis. It's a legal regulatory issue. I don't think that it really speaks to the scientific issue.

Q. I suppose I ought to read it into the

record again. The passage we were referring to was, again, from Page 34,479.

"Epidemiologic studies demonstrate that benzene exposure can cause leukemia, multiple myeloma, and perhaps other hematopoietic and lymphatic cancers. Aplastic anemia and several other blood diseases are also known to be caused by benzene exposure. Observations related to the above findings have been demonstrated by a number of high quality epidemiologic studies and case reports, such as those by Rinsky, Wong, Ott, Decoufle, Infante, Aksoy, Vigliani and others."

That's the passage we were referring to. Whether you want to talk about it being authoritative or not, you disagree with that conclusion; is that correct, Doctor?

A. I disagree with some of those conclusions; by no means all of them.

MS. ARRAS: You're not going to read the rest of that paragraph into the record?

MR. FLERLAGE: No. I don't think I did yesterday. No, not unless you want to.

BY MR. FLERLAGE:

Q. Mr. Stelly was a pipefitter, correct?

A. Yes.
Q. We went through this to a limited extent, but is there any way you can characterize whether he engaged in the repair or maintenance of any chemical reactors, valves, fittings or pipes?
A. To the best of my recollection, he describes repairing pipes.
Q. And not specific fittings or anything, valves, process piping, anything like that?
A. At this point, not that I recall.
Q. Did either Mr. Stelly or Mr. LeBlanc talk about safety precautions which they may have been offered or took in any of the plants we're involved with?
A. I recall some statements to that effect.
Q. Which were they?
A. I would have to refer back to the deposition to be accurate, but I do recall some discussion of that.
Q. Did that enter into your opinion-making in this case at all, whether or not they wore safety devices or took precautions?
A. The issue of exposure and dose is not relevant to the question of causation in my

opinion. From that standpoint, I did not require in reaching my opinion to have an abject knowledge of their specific exposure, because I don't think it's relevant.

As I mentioned before, there is nothing within the information I have read that would allow me to assess any exposure, but by the same token, it's not significant with respect to my opinion of causation between benzene and multiple myeloma.

Q. Did you need either one of these gentlemen's occupational exposure backgrounds to form a opinion in this case?

A. To the extent that it provides the basis for understanding what the allegations are, yes, but in terms of reaching an opinion on causation and what the literature says with respect to causation, no.

Q. Would it be fair to say that given the disease process, multiple myeloma, it doesn't matter how much exposure to benzene either one of these gentlemen may have had, in your opinion?

A. Based upon the literature today, that's correct. The actual exposure is not at issue here. That's not the issue in multiple myeloma.

Q. Doctor, I think I only have one other

area. In the Ellis deposition on December 17, 1991, on Page 55, and let me read it into the record and then I will give it to you, you were asked the following question on Page 55, Line 18.

"Do you believe there is more evidence that benzene causes multiple myeloma than the lymphoid leukemias?"

And your answer at Line 21 was "I would say yes, but I would also like to explain. I don't think there is sufficient evidence to indicate that benzene causes multiple myeloma, so we are talking about grades of insufficient evidence. I believe there is no evidence that benzene is associated with lymphoid leukemias." Let me show you that to make sure I read it right.

A. Okay. I recall that.

Q. Is that still your testimony today, or has that changed?

A. I would say that, in general, my testimony is consistent with this, to the extent that I have strengthened my opinion with respect to the lack of evidence for multiple myeloma, following my reading of the literature that currently exists.

At the point in time that I said

this, I was referring specifically to the Tabershaw-Cooper study and to the Rinsky study as being the basis for this statement.

As I mentioned earlier, at the request of Ms. Arras, I reviewed all the literature that we have here, and I think that it strengthens my conclusion that there is no evidence that would support the conclusion that multiple myeloma is associated with benzene.

But by the same token, again, if we are going to talk about grades of insufficiency, I think that this statement still is true.

Q. Okay. I have no further questions. Thank you.

MR. FLERLAGE: Read and sign?

MS. ARRAS: Yes.

(DEPOSITION CONCLUDED)

C E R T I F I C A T E

I, JULIE L. SAMFORD, Certified Shorthand Reporter, do hereby certify that the witness, after having been first duly sworn to testify to the truth, the whole truth, and nothing but the truth, did testify as hereinabove set forth;

That the testimony was reported by me in shorthand and transcribed under my personal direction and supervision, and is a true and correct transcript, to the best of my ability and understanding;

That I am not of counsel, not related to counsel or the parties hereto, and have no personal interest in the outcome of this event.

_____
JULIE L. SAMFORD
Certified Shorthand Reporter